LONG CASES IN
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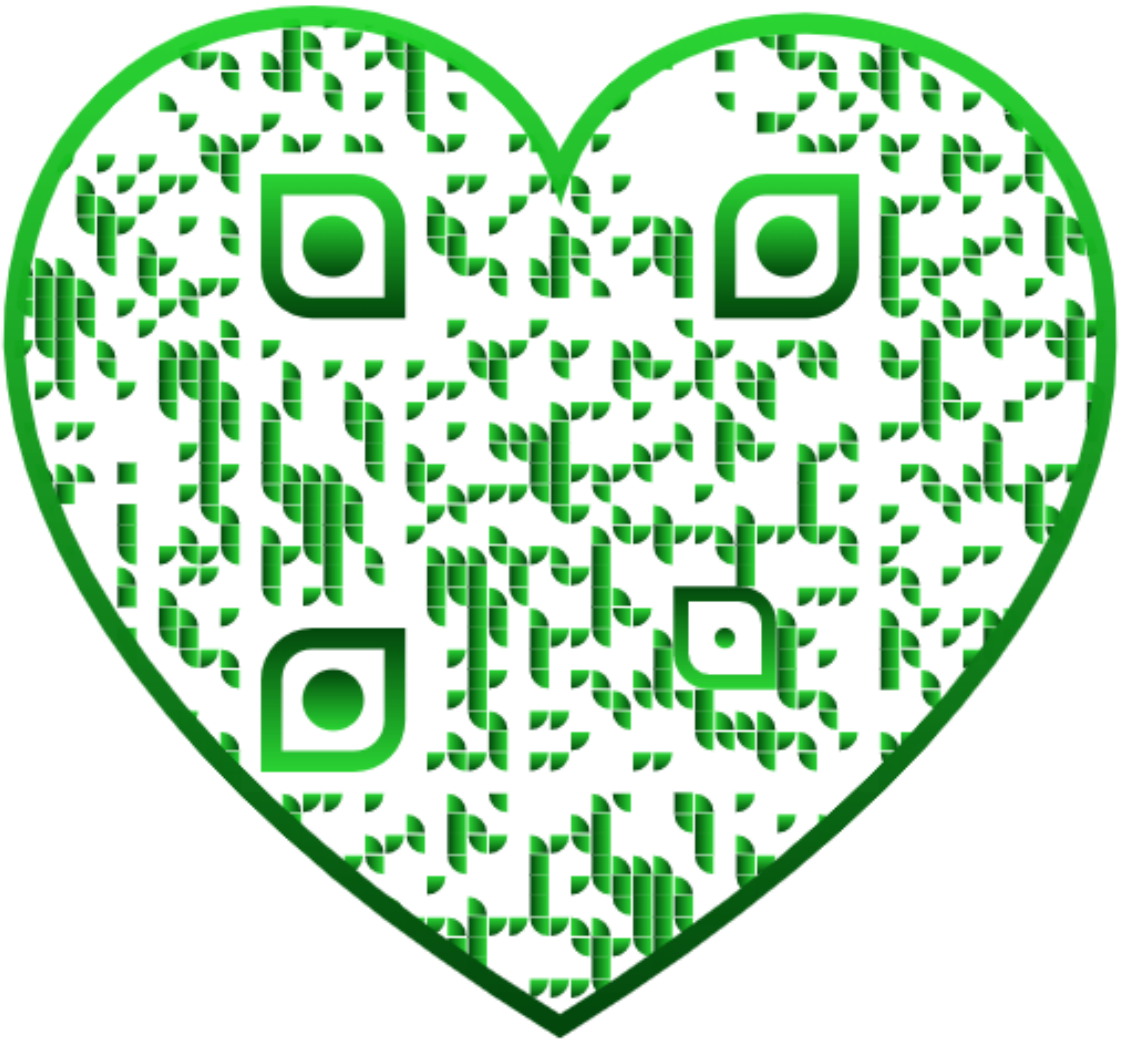

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LONG CASES IN CLINICAL MEDICINE

(Concerned with long cases, their presentation, related questions, answers and discussions)

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Foreword
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"He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all."

—Sir William Osler

Dedicated to

My Parents,
Wife
and
Children

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Foreword

This is my pleasure and great honor to write a few words about *Long Cases in Clinical Medicine*. Professor Abdullah has written an excellent "made easy" book that will help both undergraduate and postgraduate students prepare themselves in a systematic manner. It is easy to understand, concise, and will help to learn many aspects of medicine. This will reflect the diseases of the region.

Medicine is a vast subject and ever-changing science, expanding and progressing day by day. New information is emerging all the time, making the textbooks bigger and harder to assimilate. Textbooks are a good source of knowledge, but many students, in spite of hours of tedious work, are often unable to acquire all the necessary information in a concise way.

Dr Abdullah has admirably succeeded in fulfilling this gap by preparing such a book in a concise and methodical way. This book is certainly the first of its kind to fulfill the long demand of students and doctors. I have no doubt that this book will be of immense benefit for the students who are appearing in any postgraduate and undergraduate examination in clinical medicine. This book has an excellent outline regarding presentation of long cases, answers of relevant questions and a brief discussion.

When I was a new student in clinical medicine, I found it difficult while talking to the patient, taking the history, physical examination, coming to the diagnosis, etc. I think every new student in clinical medicine used to feel the same problem. There is no book or clinical methods that will fill these difficulties. In that respect, I strongly appreciate and feel that this book will really be a good guide, written in a concise and rational manner that will greatly help the undergraduate students to establish the foundation of clinical medicine with ease and confidence.

I heartily appreciate and praise the author's effort, hard work, sincere endeavor, enthusiasm and patience in bringing out this book in a beautifully designed way for the benefit of the learners in medicine.

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Preface

By the good grace of Almighty, I have succeeded to bring out the first edition of *Long Cases in Clinical Medicine*.

Long cases are an integral part of any examination in medicine. The idea is to assess the candidate's ability of gathering adequate information from thorough medical history and physical examination, interpreting them to come up with a probable diagnosis and formulating a management plan. A sound knowledge of medical science, optimum clinical skills, good interpersonal communication and adequate time management are all needed. A good preparation and adequate practice are vital for success.

From my experience as a teacher and an examiner in medicine, I feel that many candidates, even brilliant ones, fail to succeed in long cases due to lack of adequate technique of taking history from the patient, analysis of symptoms, inapt presentation and inability to answer questions related to the case. In spite of good theoretical knowledge, many of them are unable to effectively communicate with the patient. This is because they do not prepare themselves in an examination-oriented manner. It is important to acquire knowledge from textbooks, but it is equally vital to know what to expect in examinations, how to face them and to practice with that in mind. Goal-based preparation, systematic practice and repeated exposure to different cases and rehearsal of presentation in front of others is the secret to success. With this in mind, I have written this book to help students prepare themselves in an examination-oriented manner.

This book has been written to entertain a wide variety of readers from medical students to postgraduate examinees. It includes a complete outline of a comprehensive medical encounter including history taking and physical examination. It also gives valuable tips regarding interpretation of various clinical features to make a diagnosis. Successive chapters include long cases arranged according to body systems. In each case, the history and examination is presented first followed by the clinical diagnosis and possible differentials. Then the relevant questions and answers are provided.

The best way to get the most out of this book would be to practice a real case in the ward and then go through the relevant example given in the book. Students should notice how the case has been presented, the important clinical points that are mentioned and then familiarize themselves with the relevant questions and answers. They can make small groups where one will present a case in front of others and then answer questions asked by them. This will help them to be confident and fluent during the real examination.

In examination, a patient may have a single disease, or may be suffering from multiple diseases. For the purpose of preparation and simplicity, I have prepared this book using a prototype single case of a disease condition.

I do not claim that this book is enough for the whole clinical medicine and one should consult standard textbooks for learning. But for examination purpose, this book will be a valuable tool for optimum preparation.

A candidate needs to prove that he is not only knowledgeable but also competent. I hope that this book will help to promote such an approach.

I would like to invite constructive criticism from valued readers of this book, so that any error or omission may be corrected in future edition.

ABM Abdullah

Acknowledgments

I would like to take the opportunity to extend my sincere gratitude to **Professor Pran Gopal Datta** MCPS, ACORL (Odessa), PhD (Kiev), MSc in Audiology (UK), FCPS, FRCS (Glasgow-UK), Vice-Chancellor, Bangabandhu Sheikh Mujib Medical University, for his encouragement and valuable suggestions in preparing this book.

I am also highly grateful to Dr Ahmed-al-Muntasir-Niloy for the computer composing and graphic designing of the entire book. He has also gone through the whole manuscript and made necessary corrections and modifications. I can, without any hesitation, mention that he has worked as the co-author.

I must acknowledge the contributions of my colleagues, doctors and students who were kind enough to help me in writing such a book of its kind. They are always a source of my inspiration and encouragement.

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I must be grateful to my students who were repeatedly encouraging and demanding to write such a book.

Last but not least, I must express that no amount of appreciation is sufficient for my wife and children, whose untiring support and sacrifice has made it possible to bring such a book in the light of the day.

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"The good physician treats the disease; the great physician treats the patient who has the disease."

—Sir William Osler

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CHAPTER 1

Proforma of a Long Case

"Observe, record, tabulate, communicate. Use your five senses. Learn to see, learn to hear, learn to feel, learn to smell, and know that by practice alone you can become expert." **—Sir William Osler**

- **Brief Discussion and Elaboration about Physical Examination 12**
- **How to Approach a Long Case 23**
- **How to Proceed with a Long Case 26**
- **Systemic Inquiry 29**
- **Description (or Elaboration) of Symptoms 32**

HISTORY OF THE PATIENT

- Name, age, sex, address, marital status, occupation, religion
- Date of admission
- Date of examination
- Chief complaints (in chronological order, from longest to shortest duration)
- History of present illness
- History of past illness (including any operation)
- Family history
- Personal history
- Socioeconomic history
- Psychiatric history
- Drug and treatment history
- History of allergy (to drugs, diet or anything else, skin rash associated with allergy, treatment taken for allergy)
- History of immunization
- Menstrual and obstetric history (in female)
- Other history – Travelling to other places or abroad, working abroad (may be related to hepatitis B, HIV, etc.), contact with TB patient (mention, if relevant).

PHYSICAL EXAMINATION (INCLUDES GENERAL AND SYSTEMIC EXAMINATION)

General Examination

- Appearance
- Build
- Nutrition
- Decubitus
- Cooperation
- Anemia
- Jaundice
- Cyanosis
- Clubbing
- Koilonychia
- Leukonychia
- Edema
- Dehydration
- Bony tenderness
- Pigmentation
- Lymph nodes
- Thyroid gland
- Breasts
- Body hair
- Pulse
- Blood pressure
- Temperature
- Respiration

- Others (if relevant) – Neck, axilla, head (alopecia, large or small). Skin lesion (if any, such as butterfly rash in face, rash in body, scratch mark).

Systemic Examination

Cardiovascular System

1. Pulse:
   - Rate
   - Rhythm
   - Volume
   - Character
   - Condition of the vessel wall
   - Radio-femoral delay
   - Radio-radial delay
2. Neck veins (JVP), hepatojugular reflux (if needed)
3. Blood Pressure.

Precordium (Sequentially—Inspection, Palpation, Percussion and Auscultation)

Inspection:

- Any deformity of the chest
- Visible cardiac impulse
- Other impulses (epigastric, suprasternal, supraclavicular or other impulse)
- Any scar mark (midsternal or thoracotomy)
- Pacemaker or cardioverter defibrillator box (mention, if any).

Palpation:

1. Apex beat:
   - Site (that intercostal space)
   - Distance from midline (in cm)
   - Nature (normal, tapping, heaving, thrusting, diffuse or double apex).
2. Thrill:
   - Site (that intercostal space, apical or basal or other site)
   - Nature (systolic or diastolic or both).
3. Left parasternal heave
4. Palpable P_2
5. Epigastric pulsation.

Percussion:

- Area of cardiac dullness (Not a routine. However, it is important to diagnose pericardial effusion, where area of cardiac dullness is increased and in emphysema, where area of cardiac dullness is obliterated).

Auscultation:

1. 1st and 2nd heart sounds
2. Other heart sounds (3rd and 4th)

3. Murmur:
   - Site
   - Nature (systolic, diastolic or both)
   - Radiation (towards left axilla or neck)
   - Relation with respiration, posture (in left lateral position with breathing hold after expiration or bending forward with breathing hold after expiration)
   - Grading (1, 2, 3...)
4. Added sounds (pericardial rub, opening snap, ejection click, metallic plop)
5. Auscultate back of the chest (to see bilateral basal crepitations in pulmonary edema).

Respiratory System

Examination of the chest (systematically—inspection, palpation, percussion and auscultation).

Inspection:

- Shape of the chest
- Deformity (flattening of the chest, kyphosis, scoliosis, etc.)
- Drooping of the shoulder
- Movement of the chest
- Intercostal space (indrawing or fullness)
- Visible impulse
- Visible or engorged vein (if present, see flow)
- Others (scar marks, suprasternal and supraclavicular excavation, prominent accessory muscles, gynecomastia, needle puncture mark, tattooing, radiation mark).

Palpation:

- Position of trachea
- Apex beat
- Chest expansion
- Chest movement (symmetrical or asymmetrical)
- Tracheal tug
- Cricosternal distance
- Vocal fremitus
- Local rib tenderness.

Percussion:

- Percussion note
- Liver dullness
- Area of cardiac dullness (not done routinely, only if emphysema is suspected).

Auscultation:

- Breath sound
- Vocal resonance
- Added sounds (rhonchi, crepitations, pleural rub, post-tussive crepitations).

Note

Always examine the back of the chest, systematically.

Gastrointestinal System

(Always start examining from mouth and pharynx, then abdomen).

Mouth and pharynx:

- Lips
- Teeth and gum
- Oral mucous membrane
- Tongue
- Palate and movement of soft palate
- Tonsils
- Fauces.

> **Note**
>
> Look for pigmentation, white patch, ulceration.

Abdomen (Examine Systematically—Inspection, Palpation, Percussion and Auscultation)

Inspection:

- Shape of the abdomen
- Flanks
- Movement with respiration
- Visible peristalsis
- Visible pulsation
- Umbilicus
- Engorged veins (if present, see the direction of flow both above and below the umbilicus)
- Striae
- Any scar mark
- Pigmentation
- Swelling or mass (tell the site)
- Campbell de Morgan's spot
- Groin, pubic hair and genitalia (with permission of the patient)
- Cough impulse.

Palpation:

- Superficial palpation and local temperature
- Deep palpation (tenderness, rigidity, mass)
- Liver:
  - Size (in cm)
  - Margin
  - Surface
  - Tenderness
  - Consistency
  - Upper border of the liver dullness
  - Auscultation (to see bruit or rub).
- Spleen (size in cm)
- Kidneys

- Gallbladder (if palpable, mention the size, tenderness, consistency, surface, margin)
- Fluid thrill (if ascites is suspected)
- Any mass (if present, first see whether it is intra-abdominal or extra-abdominal). Then see the following points:
  - Site
  - Size
  - Shape
  - Surface
  - Consistency
  - Tenderness
  - Mobility
  - Others: (whether pulsatile, feel for get above the swelling).
- Para-aortic lymph nodes
- Hernial orifice
- Testis (with permission of the patient)
- Per-rectal examination (though it is a part of physical examination, usually it is never done in an examination setting).

Percussion:

- Liver dullness
- Splenic dullness
- Shifting dullness (if ascites is suspected or present).

Auscultation:

- Bowel sounds
- Hepatic bruit or rub
- Renal bruit
- Bruit of aortic aneurysm
- Splenic rub
- Venous hum.

Nervous System

Higher Psychic Functions (HPF):

- Appearance
- Behavior
- Consciousness
- Memory
- Intelligence
- Orientation of time, space and person
- Emotional state
- Hallucination
- Delusion
- Speech.

Motor functions:

- Bulk of the muscle

- Tone of the muscle
- Power of the muscle
- Fasciculation
- Involuntary movement (mention the type, e.g. tremor, chorea, athetosis, hemiballismus, etc.)
- Coordination test:
  - Finger nose test
  - Heel shin test
  - Romberg's sign
- Gait and posture.

Reflexes (Superficial and Deep)

Superficial reflexes:

- Plantar reflex
- Abdominal reflex
- Corneal reflex
- Palatal reflex
- Cremasteric reflex.

Deep reflexes:

Side	Biceps	Triceps	Supinator	Knee	Ankle
Right					
Left					

Clonus:

- Ankle
- Patellar.

Others: Gordon's sign and Oppenheim's sign (both in leg) and Hoffman's sign.

Sensory functions:

- Pain
- Touch
- Temperature
- Position sense
- Sense of vibration
- Tactile localization
- Tactile discrimination
- Recognition of size and shape, weight and form of object
- Romberg's sign.

Signs of meningeal irritation:

- Neck rigidity
- Kernig's sign
- Brudzinski's sign.

Examination of cranial nerves:

- Olfactory nerve (sense of smell or hallucination of smell)

- Optic nerve:
  - Visual acuity
  - Field of vision
  - Color vision
  - Light reflex (direct and consensual)
  - Fundoscopy (see last)
- Oculomotor, trochlear and abducent nerve:
  - Ptosis
  - Squint
  - Ocular movements
  - Diplopia
  - Nystagmus
  - Pupils (size, shape, light reflex)
  - Accommodation reflex.
- Trigeminal nerve:
  - Motor
  - Sensory
  - Corneal reflex.
- Facial nerve (both sensory and motor)
- Vestibulocochlear nerve: (ask about any hearing abnormality, vertigo or dizziness or giddiness).
  - Look at the external auditory meatus (for any wax, rash)
  - Rinne's test and Weber's test.
- Glossopharyngeal and vagus nerve:
  - Look for nasal voice, nasal regurgitation, hoarseness of voice, bovine cough
  - Movement of palate
  - Gag reflex
  - Taste sensation (in posterior 1/3 of tongue).
- Accessory nerve (spinal part): see the action of sternomastoid and trapezius
- Hypoglossal nerve (look at the tongue and see):
  - Wasting
  - Fasciculation
  - Movement of tongue.

Locomotor System

Bones:

- Shape
- Swelling
- Tenderness
- Deformity
- Sinus.

Joints:

- Inspection:
  - Swelling, local muscle wasting (unilateral or bilateral), any deformity
  - Redness
  - Skin change (psoriatic patch).
- Palpation:
  - Temperature

- Tenderness
- Dry or moist
- Fluctuation
- Crepitus.

- Movement:
  - Observe the range of active movement while gently palpating the joint for abnormal clicks or crepitus
  - If restricted, gently perform passive movement and check for crepitus
  - Perform passive stretching maneuvers to detect joint instability or ligament injury (when appropriate).

Spine:

- Look for any kyphosis, scoliosis, lordosis
- Any swelling of vertebral column (local swelling, Gibbus)
- Tenderness of vertebral column
- Movement of vertebrae (perform Schober's test, if appropriate).

Examination of nerve root compression:

- Straight leg raise: With the patient lying supine, flex the hip with legs extended. Normally, up to 90° hip flexion is possible. But when there is root compression, it will be restricted (patient will feel pain in the lumbar region)

Lasegue's sign: With the knee flexed, flex the hip up to 90°. Now gently extend the knee. The patient will feel pain.

Sacroiliac joint examination:

- With the patient in prone position, apply firm pressure over the sacrum with the hand
- With the patient lying on his side, press down on the pelvic brim.

Others (according to suspicion of cause, examine the individual joint accordingly. For example, in case of rheumatoid arthritis, examine the joints of hands, wrist, feet, etc.).

Genitourinary System

Inspection:

- Scar (nephrectomy)
- Scar of transplanted kidney in the right or left iliac fossa
- Visible mass (including mass of transplanted kidney)
- Small scar of dialysis
- Abdominal distension
- Inspection of scrotum for mass or swelling or edema and penis (with permission of the patient).

Palpation:

- Renal angle
- Kidneys
- Urinary bladder.

Percussion:

- Bladder.

Auscultation:

- Renal bruit.

After completing all of the above, proceed as follows:

Bedside investigations (if applicable):

- Urine for sugar (If diabetes mellitus)
- Urine for albumin (If nephrotic syndrome)

Salient features (Present in the following manner – mentioning the name, age, hailing from, smoker or nonsmoker, diabetic or nondiabetic, hypertensive or nonhypertensive, etc. One example is given below):

Mr. X, a 50-year-old businessman, smoker, nondiabetic, nonhypertensive, hailing from … was admitted in the hospital (or presented) with the complaints of:

1. … days/months
2. … days/months
3. … days/months

Then summarize the history of present illness, past history, social and other history with important negative points in the history.

On general examination—mention the important positive and important negative findings.

On systemic examination—tell the findings of the specific system. Then tell, "other systems reveal no abnormality".

My diagnosis is … (Tell the diagnosis if it is possible).

If the diagnosis is not clear, then tell in the following manner—"With this history and physical findings, I can tell some differential diagnoses".

Now, be ready to answer the questions asked by the examiner.

BRIEF DISCUSSION AND ELABORATION ABOUT PHYSICAL EXAMINATION

Always begin with the general examination, followed by systemic examination. Details history will suggest that system or parts of the body should be examined first.

General Examination

Remember, **"A doctor must be a good observer, like a detective"**. So, before starting general examination, look carefully from head to foot.

- **Appearance** (ill or well looking, depressed, anxious, Cushingoid, expressionless face)
- **Built** (obese, emaciated or cachexic, tall, short, normal)
- **Nutrition** (well nourished, poor, normal)
- **Decubitus** (on choice, propped up, lateral bending, Mohammedan's prayer position)
- **Anemia** (see in palpebral part of conjunctiva, tongue, palm, nails, body as a whole). Mention whether it is mild, moderate or severe
- **Jaundice** (see in sclera, under surface of the tongue, palm, body as a whole). Mention whether it is mild, moderate or severe (deep)
- **Cyanosis** (see in tip of the nose, lips, ear lobule, tongue, tip of the finger and toes). Comment whether the cyanosis is peripheral or central. Be aware of differential cyanosis (it means cyanosis in toes, not fingers)
- **Clubbing** (see fluctuation of nail base, angle between the nail and its base, curvature of the nails, look for hypertrophic osteoarthropathy by pressing the lower end of tibia-fibula or radius-ulna). Mention whether it is early clubbing, drum-stick or parrot-beak appearance. Be aware of differential clubbing (it means clubbing in toes, not fingers)
- **Koilonychia** (feel the nails for dryness, brittleness, flattening, thinning, spooning)
- **Leukonychia** (white spots in nail or white nail)
- **Edema** (in leg above the medial malleolus, in sacrum if the patient is recumbent)
- **Dehydration** (skin turgor, dry tongue)
- **Pigmentation** (exposed parts, face, neck, palmar creases, knuckles, inner side of the mouth, recent scars)
- **Lymph nodes** (examine systematically in different areas)
- **Thyroid gland** (palpable or enlarged)**.** If enlarged, examine in details
- **Breasts** (normal or enlarged or any mass)
- **Bony tenderness**
- **Body hair distribution** (including head, to see alopecia)
- **Pulse** (rate/min)
- **Blood pressure**
- **Temperature** (record in Centigrade or Fahrenheit)
- **Respiration** (number of respiration per minute, mention if any abnormality found)**.**

(Other findings, though not seen routinely, should be mentioned if present or relevant to individual cases. Examples are – xanthelasma, corneal arcus, xanthomatous nodules, skin rash, alopecia, scratch mark, rheumatoid nodule, Dupuytren's contracture, palmar erythema, Osler's node, splinter hemorrhage, Heberden's node, Bouchard's node, gangrene or nail fold infarct or nail fold telangiectasia, ulceration, wasting, skin rash or Gottron's patch, spider angioma, parotid gland enlargement, striae, Campbell de Morgan's spot, purpura, vitiligo, deformity like kyphosis, scoliosis, lordosis).

Note

Mention if the patient has any cannula, catheter, N-G tube, CV line, A-V fistula, etc. Remember to examine the lower limb to see unilateral leg swelling, DVT, differential cyanosis, clubbing, trophic ulcer or gangrene.

Systemic Examination

(From the history, once you get a clue of a particular disease, examine that system first. Then examine the other systems).

Cardiovascular System (First See Pulse, Neck Veins and BP, then Examine the Precordium)

1. Pulse (all the following features should be seen in radial pulse):
   - Rate (beat/min)
   - Rhythm (interval between two beats)
   - Volume—low, high or normal (make sure you lift the arm to see collapsing pulse)
   - Character (normal, slow rising, collapsing)
   - Condition of the vessel wall (if normal, tell, "neither thicken nor tortuous")
   - Radio-femoral delay and radio-radial delay (or inequality).

Compare all other pulses simultaneously (beware of the carotid pulse that should not be seen simultaneously). Volume and character of the pulse are better seen in the brachial and carotid artery. Collapsing pulse in aortic regurgitation and pulsus alternans in acute left ventricular failure are better seen in the radial artery.

2. Neck veins (JVP): The patient should lie at 45°.
   - Normal or engorged (internal jugular vein that lies medial to the sternomastoid). If visible, see any prominent wave. Always see hepatojugular reflux. Next, measure the height from the sternal angle (it indicates the mean pressure in the right atrium. Normally, it is at the level of the sternal angle and invisible).
   - Other signs in neck:
     - Tall, sinuous venous pulse, oscillating up to the ear lobule (indicates prominent V wave, found in tricuspid regurgitation)
     - Dancing carotid pulse (called Corrigan's sign found in aortic regurgitation)
     - Vigorous arterial pulsation in neck (found in coarctation of aorta)
     - Other pulsation in neck (carotid aneurysm or subclavian artery aneurysm).
3. Blood pressure (BP):
   - Measure BP (normal or high).
     - Low systolic, normal diastolic and narrow pulse pressure (found in aortic stenosis)
     - High systolic, low diastolic and wide pulse pressure (found in aortic regurgitation)

(If needed, see in both arms, also in standing and lying to see postural hypotension).

examination of Precordium

Inspection:

- Deformity of the chest wall (kyphosis, scoliosis, lordosis, pectus excavatum or carinatum)
- Visible cardiac impulse (visible apex beat)

- Other impulses: epigastric, suprasternal, supraclavicular
- Any scar mark: in the midline (valve replacement or coronary artery bypass), thoracotomy scar (valvotomy in mitral stenosis)
- Pacemaker or cardioverter defibrillator box may be seen (mention, if any).

Palpation:

1. Apex beat:
   - Site (localize the intercostal space. Beware of dextrocardia)
   - Distance from the midline (in cm)
   - Nature (normal, taping, heaving, thrusting, diffuse or double apex beat).
2. Thrill:
   - Site (apical, basal or any other space)
   - Nature (systolic or diastolic, by feeling the carotid pulse at the same time. If coincides with carotid pulse, it is systolic and if it does not coincide, it is diastolic).

Note

Always feel apical and basal thrill. Apical thrill is best felt by turning the patient to the left lateral position with breathing hold after expiration (apex comes close to the chest wall). Basal thrill is best felt with the patient sitting up and bending forward, breathing hold after expiration (base of the heart comes close to the chest wall).

3. Left parasternal heave: Place the flat of right palm in left parasternal area and feel by giving gentle sustain pressure (presence of left parasternal heave indicates RVH)
4. Palpable P_2 (in left second intercostal space): It indicates pulmonary hypertension
5. Epigastric pulsation.

Percussion:

Usually not done, may be helpful to diagnose pericardial effusion (area of cardiac dullness is increased) and emphysema (cardiac dullness is obliterated).

Auscultation:

1. First and second heart sounds in all four areas (mitral, aortic, pulmonary and tricuspid areas). At the same time, palpate the right carotid pulse with thumb simultaneously. **1st heart sound** coincides with carotid pulse, but **2nd sound** does not (comes before or after). See also other heart sounds, if present (3rd and 4th).
2. Murmur:
   - Site (apical, parasternal, aortic or pulmonary area)
   - Nature—systolic (pansystolic or ejection systolic), diastolic (mid diastolic or early diastolic)—by feeling carotid pulse at the same time (systolic coincides with carotid pulse and diastolic does not coincide)
   - Radiation (pansystolic murmur to left axilla, ejection systolic murmur to neck)
   - Relation with respiration (right sided murmur increases on inspiration and left sided murmur increases on expiration)
   - Grading of murmur (e.g. 2/6, 4/6).
3. Added sounds (pericardial rub, opening snap, ejection click, metallic plop.
4. Others:
   - Auscultate the back of the chest for crepitations (found in pulmonary edema).

- Palpate the liver (enlarged tender liver in CCF, pulsatile liver in tricuspid regurgitation)
- Splenomegaly (may be found in infective endocarditis).

Note: Remember the following points:

- If MDM—mid diastolic murmur is present in apex, always ask the patient to turn in left lateral position with breathing hold after expiration and auscultate with the bell of the stethoscope (MDM will be more prominent)
- If EDM—early diastolic murmur is present, ask the patient to sit up and bend forward, hold breathing after expiration. Now auscultate (EDM will be more prominent)
- If PSM—pansystolic murmur is present, put your stethoscope in left axilla to see the radiation
- If ESM—ejection systolic murmur is present, put your stethoscope in right carotid to see radiation.

Respiratory System

(Examine the chest from both front and back – **I**nspection, **P**alpation, **P**ercussion and **A**uscultation).

Inspection:

- Shape (asymmetry, deformity, barrel shaped, pectus excavatum or carinatum, kyphoscoliosis), flattening and drooping of the shoulder (due to fibrosis or collapse)
- Movement (unilateral or bilateral restriction), upward movement (in emphysema). See paradoxical inward motion of abdomen during inspiration with the patient in supine position (indicates diaphragmatic paralysis)
- Intercostal space (fullness, indrawing of lower ribs, Harrison's sulcus)
- Scar mark (thoracotomy scar, thoracoplasty, radiation marks)
- Visible impulse (cardiac, epigastric)
- Visible, engorged vein in chest (SVC obstruction). If present, see the flow
- Others: Suprasternal and supraclavicular excavation, prominent accessory muscles, gynecomastia, needle puncture mark, tattooing, bandage or gauge with tape.

Palpation:

- Position of trachea (deviated to the right or left or central). Normally, it is slightly deviated to the right
- Apex beat (shifted or not)
- Vocal fremitus (normal, increased, decreased or absent)
- Chest expansion (normal or reduced)
- Tracheal tug (descent of the trachea during inspiration. Examine by placing fingers over the trachea. It indicates hyperinflation of lung)
- Cricosternal distance: It is the distance between the suprasternal notch and cricoid cartilage (normally 3 fingers or more. If it is less, indicates hyperinflation)
- Rib tenderness (due to trauma or fracture, secondary deposit), tenderness in costochondral junction (due to Tietz's syndrome).

Percussion:

- Percussion note (normal resonance, hyper-resonance, stony dull, woody dull, impaired)
- Area of liver dullness (normally in 5th ICS in the right mid-clavicular line. It is obliterated or lower down because of emphysema or severe asthma).
- Area of cardiac dullness (obliterated because of emphysema or severe asthma).

Auscultation: (Turn the head of the patient to the left side and tell him, "Keep your mouth open, take deep breath in and out for me". Place the stethoscope. Auscultate in both right and left sides alternately).

- Breath sound (normal vesicular, vesicular with prolonged expiration, bronchial, diminished vesicular or absent)
- Vocal resonance (normal, increased, decreased or absent)
- Added sounds –
  - Rhonchi (high or low pitched, localized or generalized)
  - Crepitations (fine or coarse or end inspiratory. If crepitations are present, ask the patient to cough and auscultate again whether the crepitations are diminished, absent or same). Post-tussive crepitations that appear after cough may be found in tuberculosis
  - Pleural rub.

Ask the patient to sit forward, examine the back of chest systematically.

Finally see the following points:

- If your diagnosis is COPD, see FET (forced expiratory time), by asking the patient to exhale forcefully after full inspiration, while you listen by placing your stethoscope over the trachea. Normally, it is < 6 seconds. If > 6 seconds, indicates airway obstruction
- If any sputum cup is available nearby, look at the sputum and comment on it.

Gastrointestinal System

Mouth and pharynx:

- Lips (cyanosis, inflammation, any swelling, ulceration, angular stomatitis, pigmentation)
- Teeth (number, infection at the root, tartar, dental caries, Hutchinson's teeth)
- Gum (color, signs of inflammation, swelling or hypertrophy, ulceration, bleeding)
- Palate, movement of soft palate
- Tongue (color, papillae, dry or moist, ulceration, inflammation, presence or absence of fur, coating, white patch, candidiasis)
- Oral mucous membrane (colour, pigmentation, inflammation, ulceration, swelling, opening of the parotid duct)
- Tonsils (inflammation, swelling, pus formation, ulceration, membrane)
- Fauces (see any patch, redness, ulceration).

Abdomen (**I**nspection, **P**alpation, **P**ercussion and **A**uscultation).

Inspection:

- Shape of the abdomen—normal or distended or shrunken (scaphoid). If distended, whether generalized or localized (in epigastrium, right or left hypochondrium or iliac fossa, central part)
- Movement of the abdomen—ask the patient to take deep breath in and out, inspect from either leg or head end (to see whether the movement is equal in all sides)
- Visible peristalsis (present or absent)
- Visible pulsation (in the epigastrium)
- Umbilicus (inverted or everted)
- Visible veins—tell where (central part, flank, below or above the umbilicus, around the umbilicus). If present, **see the flow** both above and below the umbilicus
- Striae—tell where (color, size, vertical or horizontal)
- Any scar mark (because of surgery, trauma), fistula (Crohn's disease), stoma (colostomy, ileostomy, ileal conduit)

- Pigmentation (linea nigra from below umbilicus, erythema ab igne)
- Mass or swelling (tell the site, see whether it is intra-abdominal or extra-abdominal)
- Campbell de Morgan's spot (small, red, nodular lesion, common in middle age or elderly)
- Finally look to the groin (ask the patient to cough), pubic hair, genitalia (with permission of the patient).

Palpation:

- Inquire any pain in abdomen (examine that part last) and tell the patient, "Please tell me, if I hurt you"
- Ensure that your hand is warm, put the palm gently rather than the tip of the finger, keeping the hand flat on the abdominal wall with a gentle flexion of metacarpophalangeal (MCP) joints
- Better if you are in horizontal position with the patient, wrist and forearm in the same horizontal plane, by bending or kneeling by the side of the patient
- During palpation, look to the patient's face to see whether he or she **"winces"** with pain
- If ascites, do not forget to palpate by **dipping technique**.

1. First, perform superficial palpation—feel for rigidity or any mass. Hard periumbilical lymph node (called **"Sister Marie Joseph's nodule"** is highly suggestive of metastasis from pelvic or GIT primary tumor)
2. Tenderness (occasionally rebound tenderness may be seen—press the abdomen slowly, then release suddenly. Pain may be present that indicates peritonitis)
3. Liver—start from right iliac fossa, ask the patient, "turn your face to left side, keep your mouth open, take deep breath in and out". Press and proceed during inspiration and look at the patient's face. If the liver is palpable, see the following points:
   - Measure in cm from the costal margin in the right mid-clavicular line. If left lobe is enlarged, measure from xiphoid process. Always measure with tape (not with fingers)
   - Margin (round or smooth or sharp)
   - Tenderness (tender or nontender)
   - Surface (smooth or irregular)
   - Consistency (soft or firm or hard)
   - Upper border of the liver dullness (using heavy percussion, but percussion of lower border using light percussion)
   - Auscultation (to hear bruit or rub).

Note

Pulsatile liver may be present. In such case, put your left hand on the back, right hand over the liver, press gently and see movement of right hand).

4. Spleen (keep your left hand in lowermost part of left side of chest posterolaterally with slight pressure. Starting from the right iliac fossa, ask the patient, "turn your face to left side, keep your mouth open, take deep breath in and out". If it is not felt, turn the patient halfway toward right and palpate again. Once the spleen is palpable, see the following points:
   - Measure in cm along its long axis from costal margin in anterior axillary line towards right iliac fossa (also from costal margin in left midclavicular line downward)
   - Feel splenic notch (definitive sign of splenomegaly)
   - See – get above the swelling of spleen (insinuate right index finger between spleen and left costal margin)
   - See margin, surface, consistency and tenderness
   - Percuss over the spleen and continue up to left lower part of chest (to see the continuation of splenic dullness)
   - Auscultate over the spleen (to see splenic rub)

5. Palpate both right and left kidney (by ballottement)
6. Gallbladder
7. Any mass (see below)
8. Feel for para-aortic lymph nodes
9. Urinary bladder
10. Palpate the hernial orifice (ask the patient to cough, see and palpate)
11. Palpate the testis (with permission of the patient)
12. Finally per-rectal examination (tell if the examiner ask). **Never done in examination.**

Percussion:

- Usually a light percussion is done. Note the normal tympanic sound or any dullness
- If there is suspicion of ascites, elicit shifting dullness
- Fluid thrill (only necessary, if there is tense ascites).

Auscultation:

- Auscultate (normal bowel sound, increased borborygmi or reduced or absent bowel sound)
- Over liver (hepatic bruit or rub)
- Renal bruit (2 cm above the umbilicus and lateral to mid line)
- Bruit of aortic aneurysm (if any)
- Splenic rub (rarely present)
- Venous hum (heard between xiphisternum and umbilicus). It is a continuous, low pitch soft murmur. Presence of venous hum indicates portal hypertension (rare finding). It is because of large volume of blood flowing in umbilical or paraumbilical vein in falciparum ligament due to portosystemic shunt.

Note

When venous hum is present with prominent veins in anterior abdominal wall, it is called 'Cruveilhier-Baumgarten syndrome'.

If you get any mass, see the following points:

First, see whether it is intra-abdominal or extra-abdominal. Ask the patient to raise his head and press over the forehead. Now see and palpate the mass again. If it disappears or less prominent, it is intra-abdominal. If it is more prominent, likely to be extra-abdominal.

Next see the following points of a mass:

- Site
- Size
- Shape (round, regular or irregular)
- Surface (smooth or irregular)
- Consistency (soft, firm or hard)
- Tenderness
- Mobility (mobile or fixed).

Note

A fixed mass that does not move with respiration, suggest a retroperitoneal mass (such as retroperitoneal sarcoma) or colonic mass.

Higher psychic functions (HPF):

- Consciousness (conscious, semiconscious, unconscious or drowsy)
- Appearance and behavior (normal or violent)
- Memory – Recent and past (intact or not)
- Intelligence (normal or less)
- Orientation of time, space and person (normal or absent)
- Emotional state (normal or labile)
- Hallucination and delusion (present or absent)
- Speech (normal or dysarthria or aphasia or dysphasia or aphonia).

Motor functions:

- Bulk of the muscle (normal or wasted or hypertrophied)
- Tone of the muscle (normal, hypotonia or hypertonia)
- Power of the muscle (normal or diminished, mention the grading of weakness)
- Involuntary movement (present or absent. If present, mention the name, e.g. tremor, chorea, athetosis, etc.)
- Coordination:
  i. For upper extremity—finger nose test
  ii. For lower extremity—heel shin test
- Romberg's sign (positive or absent)
- Gait (mention the specific type of gait).

Reflexes:

1. Superficial reflexes:
   - Plantar reflex (normal flexor, extensor or equivocal).
   - Abdominal reflex (absent or exaggerated)—elicited by stroking upper and lower quadrant of the abdominal wall of each side. If present, there is contraction of abdominal muscles (It represents 7th and 12th thoracic segments)
   - Corneal reflex (present or absent)
   - Palatal reflex (present or absent)
   - Cremasteric reflex (present or absent)—elicited by stroking skin at upper and inner part of thigh. Normal response is an upward movement of testicle (It represents L_1 and L_2).
2. Deep reflex (mention whether it is normal, exaggerated, reduced or absent):

Side	B (Biceps)	T (Triceps)	S (Supinator)	K (Knee)	A (Ankle)
Right					
Left					

3. Clonus (sustained clonus indicates upper motor neuron lesion)-
   - Ankle
   - Patellar
4. Other reflexes:
   - Hoffman's sign (elicited by briskly flicking down the patient's tip of the middle finger with the examiner's thumb and index. If there is flexion of thumb or all fingers, it is positive. It indicates extensive upper motor neuron lesion)

- Gordon's sign (elicited by pinching the calcaneus tendon. If present, there is extensor plantar response)
- Oppenheim's sign (elicited by squeezing the calf or pressing heavily along the inner border of the tibia. If present, there is extensor plantar response).

Sensory functions:

1. Superficial sensations (normal, reduced or absent):
   - Touch (with cotton)
   - Temperature (with both cold and warm)
   - Pain (with pin).
2. Deep sensations:
   - Deep pain (elicited by squeezing a distal muscle or Achilles tendon. This sensation is particularly disturbed in tabes dorsalis)
   - Tactile localization
   - Tactile discrimination.
3. Position sense (intact or impaired)
4. Vibration sense (normal or decreased)
5. Recognition of size, shape, weight and form of object
6. Romberg's sign (positive or absent).

Signs of meningeal irritation:

- Neck rigidity—Normally chin can be flexed passively to touch the chest. It is not possible, if neck rigidity is present.
- Kernig's sign—Flex the knee and hip. Then gradually extend the knee. If meningeal irritation is present, patient will complain of pain (because of spasm of hamstring muscle).
- Brudzinski's sign—It is elicited with the patient in supine position and is positive when passive flexion of the neck results in spontaneous flexion of the hips and knees.

Examination of cranial nerves:

Ask the patient to sit at the edge of bed, face to face. See any obvious finding (ptosis, squint, asymmetry of face, dribbling of saliva). Now, examine the individual cranial nerve as follows:
1st Olfactory nerve:

- Examine the nasal cavity with a torch light to see any DNS, polyp
- Sense of smell (ask the patient, "Do you have any difficulty in your sense of smell?" Then examine the sense of smell, ideally by using a perfume. Put in each nostril and ask, "Do you get the smell?").

2nd Optic nerve (ask the patient whether he uses any glass. If so, ask to put it on and do the examination. Remember, each eye should be examined separately).

- Visual acuity: Both distant and near vision should be examined. Ideally, Snellen's chart should be used. If not available, proceed as follows:
  1. Distant vision—ask the patient, "look at the wall clock. What is the time now?" "Look at the window. How many rods in the window?"
  2. Near vision—tell the patient "read the newspaper or any small object".
- Color vision: Ideally it should be done with Ishihara chart. If not available, show different colors to the patient and ask, "what color is it?"
- Field of vision: Sit opposite to the patient, one meter apart at a same plane. Test each eye separately in the following way:

1. To examine right eye, ask the patient, "cover your left eye with left hand gently, look steadily at my left eye". You should cover your right eye. No one should move the eye and should look each other's tip of the nose.
2. Hold your index finger midway and from periphery, bring toward the center until you see it. Ask the patient "do you see my finger? Tell me when you see it."
3. If patient fails to see, continue to bring the finger and ask him, "tell me when you can see".
4. In this way, see in horizontal, upper and lower quadrant (temporal field).
5. Then, see nasal field in the same way.
6. Change your hand and repeat in other eye in the same manner.

- Test of central scotoma—Use a red headed pin, move it from temporal side to nasal side in the midway. Ask the patient, "Do you see it? Tell me, when it disappears".
- Fundoscopy (should be done at the end).

3rd, 4th and 6th Oculomotor, trochlear and abducent nerves:

- Look for ptosis or squint
- Ocular movements:
  1. Ask the patient, "Look at my finger. Follow it with your eyes with head fixed"
  2. See movements in horizontal and vertical directions like the pattern **"H"**
  3. See nystagmus. At extreme gaze, ask, "Do you see one or two fingers (diplopia)?"
- Pupils: size, shape, light reflex (both, direct and consensual—put light directly on one eye and see in other eye)
- Accommodation reflex (Ask the patient to look at a distant object. Then put your finger in front of his or her eyes. Now ask, "Look at my finger". See the movement of the eyeball and also pupil).

5th Trigeminal nerve (test both motor and sensory):

- Motor:
  1. Look for wasting of masseter and temporalis
  2. Ask the patient to clench his teeth and palpate the muscles. Then ask him to open the mouth, while you try to keep it closed (test for pterygoids). If paralysis is on one side, muscle of that side is less prominent and jaw deviates toward the side of lesion
  3. See jaw jerk (exaggerated or not).
- Sensory:
  1. Test along 3 divisions (ophthalmic, maxillary and mandibular) of nerve on each side using cotton and pin with eye closed
  2. See corneal reflex with a wisp of cotton. Touch the cornea (not conjunctiva), see if there is reflex blinking (afferent or sensory component is mediated by ophthalmic division of trigeminal nerve and efferent or motor component is mediated by facial nerve).

7th Facial nerve (perform both motor and sensory tests):

- Look at the face and see the following (which are present in 7th nerve palsy):
  1. Facial asymmetry and affected eye appears open and wide
  2. Drooping of corners of the mouth (unilateral or bilateral)
  3. Nasolabial fold (less pronounced).
- Motor tests:
  1. Ask the patient to look at the ceiling, keeping the head fixed and see any wrinkling of forehead, either unilateral or bilateral (frontal belly of occipitofrontalis)
  2. Ask the patient to close the eyes tightly and not to let you open it (orbicularis oculi). If failure to close, look for Bell's phenomenon
  3. Ask to whistle (orbicularis oris)

4. Ask the patient to puff cheeks out (buccinator). If paralysis, air is escaped easily on the affected side
5. Ask to show the teeth and to smile (levator anguli oris and risorius). If paralysis present, face is drawn to the healthy side.

- Sensory tests: Taste sensation of anterior 2/3rd of the tongue
- Finally, look at external auditory meatus and palate to see any rash (Ramsay Hunt's syndrome). Also, test for hyperacusis (nerve to the stapedius muscle).

8th Vestibulocochlear nerve:

- For vestibular division: Ask the patient about vertigo, dizziness or giddiness.
- For cochlear division:
  1. Look at the external ear and meatus (wax, rash)
  2. Rub hair or put the watch near the ear and ask the patient, whether he can hear or not
  3. Rinne's test and Weber's test may be necessary in some cases. Normally, air conduction is more than the bone conduction.

9th and 10th. Glossopharyngeal and Vagus nerves:

- While talking with the patient, observe any nasal voice or hoarseness. Presence of hoarseness indicates bilateral paralysis of superior laryngeal branch of vagus. If it is unilateral, usually the patient is asymptomatic
- Ask about nasal regurgitation
- Movement of the palate: Ask the patient, "open your mouth and say, **aah**". If one side remains flat and immobile, indicates paralysis of that side (soft palate is pulled to the normal side)
- Ask the patient to cough. If there is bovine cough, it indicates recurrent laryngeal nerve palsy
- Gag reflex (palatal reflex, 9th nerve): Touch the back of pharynx and see constriction
- Taste sensation in posterior 1/3rd of tongue (9th nerve).

11th Accessory nerve (spinal part):

- Ask the patient "Shrug your shoulder against resistance" (trapezius)
- Ask the patient "Turn your head to the other side against resistance". Feel sternocleidomastoid (test on both sides).

12th Hypoglossal nerve:

- Look at the tongue to see wasting, fasciculation or small and spastic or tight tongue
- Movement of tongue: Ask the patient to put out his tongue and observe the following:
  1. If small and spastic (unable to protrude)
  2. Deviation (toward the weak side).
- Ask the patient to waggle the tongue side to side. Feel the weak side.

HOW TO APPROACH A LONG CASE

"Practicing long case trains a physician to be a good clinician"

Vital parts of long cases include the following points:
- Detailed history taking
- Physical examination (general and systemic)
- Provisional diagnosis
- Differential diagnosis
- Investigations
- Management.

Proceed in a systematic way as above. Time allocation is very important. There is a fixed time given in any examination and a candidate should divide the time according to the case:
- Few minutes for history taking
- Few minutes for physical examination
- Few minutes for the formulation, plan of investigations, differential diagnosis and management
- Finally, few minutes for recapitulation of the case, as how to present the case and face the interpretation by the examiners.

Examiner usually asks:
- **Present** your case (mention the salient features)
- What is your **diagnosis**? (Remember this may be the first question. So, tell the diagnosis). Then you will be asked "**Why** do you think this is the diagnosis?" If the diagnosis is clear, then tell the brief history and important positive physical findings. From this history and physical findings my diagnosis is this. If no clear cut single diagnosis, then you can say, "with the history and physical findings, I can tell the differential diagnosis"
- What are the other possibilities (or **differential diagnoses**)? Why is it not a case of …? (Mention the points against that diagnosis)
- What **investigations** do you want to do in this case? What do you expect?
- How can you **confirm** the diagnosis?
- How will you **treat** the patient?
- What is the **prognosis**?

Remember, examiner usually interrupts at any point and you must be ready to interpret the history, physical findings, diagnosis, differential diagnosis, investigation and treatment.

Remember, during discussion of a long case, examiner usually expects or examines:
- Candidate's skill and art of taking history
- Candidate's ability to examine the patient systematically and gently
- Candidate's ability to come to a diagnosis and formulate management plan that includes investigations with interpretation of the result and treatment (symptomatic and specific).

BEFORE STARTING TO TAKE HISTORY

Careful history taking is the most fundamental and important aspect of a clinical case. Skill for good history taking can be achieved by regular practice, allocating time and having patience. Diagnosis is possible only by taking a good history, even without unnecessary investigations. A correct diagnosis is missed, not because of lack of knowledge, but because of not listening attentively to the patient or not asking the relevant questions.

- Always introduce yourself, in the following manner, "Good morning. I am Dr. … I would like to talk with you regarding your problems and if you kindly allow me, I would like to examine you" (In such a way, you can gain interest, confidence and cooperation of the patient. An intelligent patient may tell the diagnosis, treatment, etc.).
- Make a handshake and observe for any abnormality (like warm sweaty hand, tremor, slow relaxation of the handgrip).
- Check whether the patient is comfortable. Try to put the patient at ease (a good rapport may relieve distress on its own).
- Be polite, gentle, cordial and respectful to the patient (history taking is an art and beginning of doctor-patient relationship, depending on which the patient will develop confidence on the doctor).
- While you are appearing in an examination, explain to the patient that, "This is an important examination in my life. Your cooperation is very essential for me".
- While talking to the patient, watch him very carefully (patient may be anxious, apathetic or there may be obvious abnormality like myxedema, Graves' disease or Parkinsonism). Observe the nature of speech or any voice change during talking with the patient.
- Notice nonverbal clues for the diagnosis.

You must develop a good clinical eye that is extremely essential to be a good clinician. While taking history, listen to the patient carefully, and at the same time, keenly observe:

- From head to foot (gross abnormality may be obvious)
- Facial expression
- Posture
- Obvious pallor or jaundice
- Any swelling or goiter.

By observation, the diagnosis may become obvious or this will provide important clue for the diagnosis (e.g. thyrotoxicosis, myxedema, Parkinson's disease, Cushing's syndrome).

Remember the following points:

- Occasionally, if the patient is unable to give the history (such as elderly, very ill, children or aphasia), it is necessary to take history from the attendant or relative. This will also help to alert the physician, if anything is concealed by the patient. However, always try to take the patient's consent first.
- If there is possibility of drug abuse or alcoholism, ask the patient very gently and with confidentiality. Otherwise, the patient may either refuse or hide.
- Many a times, the patient tells his history in his own words. There may be irrelevant informations given by him. But you should listen attentively with patience. Unnecessary part of the history should be avoided.
- Sometimes, the patient is uncooperative, irritable or angry. In such a case, you must be more careful to make every effort to calm him down. Even if you feel irritated or angry, never show this to the patient.
- An intelligent patient may give a definite diagnosis. Even you can ask "Do you know the name of the disease from which you are suffering? What drugs are you taking? Can you mention if any procedure has been performed (e.g. aspiration of pleural fluid, peritoneal fluid, etc.)?" This will give valuable informations regarding the diagnosis, past and present problem.
- If the symptoms do not correlate with the real diagnosis, proceed with further questions. He may tell the symptoms that he has forgotten or failed to mention. However, you will have to formulate a final history of the patient before presenting to the examiner.

- Many patients may have multiple problems and multiple diagnoses. Organize to present the most important diagnosis first.
- At the end, always ask the patient, "Would you like to say anything else?"

Summary of difficulties in taking history (however, usually this type of cases are not selected for the examination):

- The patient may be very unwell (because of severe pain, vomiting, breathlessness, agitated, profuse bleeding)—take the help of the attendant.
- Unconscious, semiconscious, confused or psychiatric patient – take the history from the attendant.
- Communication difficulties (such as learning disability, deafness, mutism, aphasia or dysphasia)—take history from the attendant.
- Emotionally disturbed (angry, uncooperative)—try to calm the patient with good behavior. Let the patient relax. If the patient does not wish to speak at all, ask him – "Would you like to write it down?"
- Language may be a problem in many cases. Carefully take the history from interpreter.

HOW TO PROCEED WITH A LONG CASE

(Elaboration and description)

"A good history is the biggest and most important step towards the correct diagnosis."

After asking full name, age, sex, address, occupation, marital status, etc. start by the chief complaints.

Chief Complaints:

- Start by asking "Would you please tell me what's wrong with you?" Or, "Why are you admitted in the hospital?" Or, "What are your presenting problems?" Or, "What has been the trouble recently?"
- Try to elicit the main complaints with their time frame
- Precise chronology and sequence of events are very important
- Note the symptoms of longest duration, followed by the other symptoms in decreasing order, finally mentioning the symptom with shortest duration (suppose fever for 6 months, headache for 3 months, loss of appetite and weakness for 1 month).

History of present illness:

- Elaborate the chief complaints in details mentioning the following (mnemonic: OD PARA):
  - **O**nset—How did it start? When did it start?
  - **D**uration—How long?
  - **P**rogression—Is it progressive or static?
  - **A**ggravating factors—What makes it worse?
  - **R**elieving factors—What makes you feel better?
  - **A**nything else—Do you have anything else to mention?
- Elaboration of some common symptoms has been discussed as '**Description of symptoms'** on page no …
- Important negative parts of the history should be included if relevant.
- Information in patient's own words is more valuable, but sometimes leading questions are also necessary.
- Vague symptoms, such as "not feeling well", "head is hot", "stool is not clear", etc. should be precisely clarified. If a symptom is irrelevant, it may be ignored.
- Inquire whether the patient has been suffering from diabetes mellitus, hypertension or bronchial asthma or other chronic illness.
- Record the patient's own words, avoid using medical terms. For example, instead of "dyspnea", mention "difficulty in breathing", "vomiting of blood" should be noted instead of "hematemesis", instead of "anorexia" mention "loss of appetite".

History of past illness:

Every history of the past illness, including any event during childhood or infancy, should be recorded, as follows:

- Previous diseases with its details (duration, treatment taken, whether hospitalized).
- History of any operation, injury, trauma and procedure (catheterization, endoscopy, colonoscopy, biopsy).
- History of any investigation.
- Ask about diabetes mellitus, hypertension or other chronic illness. In case of CLD, enquire about past history of jaundice or if the patient has cardiac problem, enquire about history of rheumatic fever, hypertension, dyslipidemia.

- Ask about childhood illnesses including birth complications, immunization history, development and diseases.

Family History:

Detailed history of all the members of the family is very important. Ask about the following:

- Number of family members (parents, spouse, children, etc.)
- Their state of health. Ask – "Are they in good health?" "Do they have any illness? (e.g. ask about history of tuberculosis, hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, thyroid disorder, bronchial asthma, etc.)
- If death among family members, enquire the cause of death
- Ask about hereditary conditions (e.g. thalassemia), inquire regarding marriage among relatives (consanguinity)
- If X-linked disease is suspected, ask specifically about the health of maternal uncles.

Personal history:

Detailed personal history must be included:

- Occupation (exact nature of work)
- Marital status
- Dietary habit
- Hobby, pet keeping (cows, dog, rabbit, pigeon, etc.), interest, games, any source of entertainment
- Tea or coffee, betel nut
- Smoking (with number of sticks daily with duration) or tobacco chewing—ask technically specially in females who feel shy. If the patient is an ex-smoker, ask when he has stopped smoking and the number of sticks with duration that he used to smoke. Also, enquire any possibility of passive smoking.
- Alcohol (how much and how long, daily, weekly, occasional, place of drinking—home, outside, alone or socially). Be strategic as patient may not be forthcoming.
- History of drug abuse including alcohol, intravenous drug use, sharing of needles. Enquire about drug dependency, any social or physical problem arising from drug use. Again be careful regarding the confidentiality of the information.
- Sexual exposure or sexual practice including homosexuality, polygamy, etc. (ask strategically, without embarrassing the patient).

Socioeconomic history:

- Home and its surrounding environment—nature of house such as apartment, slum area, wooden house, living status, over-crowding, water supply and sanitation
- Office environment
- Income and employment
- Social and family relationship
- Any dependents at home? Who else at home?
- Who visits the house? (relatives, neighbor, friends).

Drug and treatment history:

- Details of drugs (previous and present)
- History of drug allergy, drug intolerance or reaction
- Treatment already received for present illness
- History of any transfusion (blood, plasma, blood product, normal saline or other fluid) received.

Immunization History:

- History of immunization is very relevant (hepatitis B, tuberculosis, tetanus).

Traveling history:

Travel or job outside the country (helpful for diagnosis of malaria, amebiasis, hepatitis B, HIV).

Psychiatric history:

Any symptoms related to anxiety, depression, dementia, hallucination, delusion, phobia, sleep pattern.

In female patient, always remember to ask 3 P –

- **P**eriod (menstrual history, such as amenorrhea, polymenorrhea, menorrhagia)
- **P**ill (oral contraceptive pill or other contraceptive method)
- **P**regnancy (obstetric history, e.g. number of child, age of last child, postpartum hemorrhage, abortion or repeated abortion).

To remember the format of history taking for long case, use the formula:

3P MAFTOSA:

- **P**resent history
- **P**ast history
- **P**ersonal history
- **M**edication (drug)
- **A**llergy
- **F**amily history
- **T**raveling history
- **O**ccupation
- **S**ocial history
- **A**nything else (psychiatric history, extra history in female patient, immunization history, etc.)

SYSTEMIC INQUIRY

(Review of Different Anatomical Systems)

Sometimes, the patient may forget to mention important symptoms or may feel it unimportant or feel shy or guilty about it. So, systematic symptom inquiry **(not mentioned by the patient)**, may give some clue to the diagnosis. Ask the questions in relation to particular anatomical systems of the body. Always begin with open questions without medical jargon. Some of the questions in different systems are given below. This may vary according to the state of patient, nature and severity of illness. Ask as follows:

General symptoms and others:

- Do you suffer from fever? If yes, ask details (see on page …).
- Do you have night sweats?
- Have you gained or lost weight? If yes, ask details (see on page …).
- Have you noticed any swelling on your body? If yes, ask details (see page …)?
- Do you feel unusually weak, lethargy, malaise or fatigue?
- Do you feel excessive sweaty or cold?
- Have you noticed any change in your complexion (pale, darkening, yellowish)?
- How is your sleep? Is there any change of sleep pattern, difficulty in getting to sleep, early awakening or feeling sleepy during the day? (Increased day time sleepiness occurs in hepatic precoma or obstructive sleep apnea).
- Do you have any skin rash or itching?

Cardiovascular system:

- Do you have chest pain or discomfort or tightness in your chest? If yes, ask details (see page …)
- Do you have difficulty in breathing? If yes, ask details (see page …)
- Do you have cough? If yes, ask details (see page …)
- Did you notice any swelling of your feet or ankle? (edema)
- Do you feel palpitation or irregular heartbeats? Do you sometimes miss a beat? Do you feel dizzy? Have you suffered from blackout?
- Do you feel pain on your legs or arms during exercise or work? (intermittent claudication)
- Do your hands or feet become blue or cold?

Note

From the history, if it is suggestive of ischemic heart disease—remember to ask about hypertension, diabetes mellitus, smoking, dyslipidemia and family history.

Respiratory system:

- Do you suffer or ever suffered from difficulty in breathing? If yes, ask details (page no. .....).
- Do you have cough? If yes, ask details (see page …).
- Did you notice blood with your sputum? If yes, ask about the amount.
- Do you feel any chest pain? (If any, ask details page no. .....).
- Have you noticed any wheezing?
- Do you snore? Or, Did anyone complain that you snore during sleep?

Alimentary and hepatobiliary system:

- Do you have heartburn?
- Do you have pain or discomfort in your abdomen? If yes, ask details (page no. .....).
- Do you feel abdominal bloating or distension?
- How is your appetite? If any change, such as loss or increased appetite, ask details.
- Do you feel nausea or vomiting? If yes ask details (see page no. .....).
- Do you feel difficulty in swallowing? If yes, ask details (see page …).
- Do you have diarrhea or constipation? If any, ask details regarding duration, frequency, amount, aggravating factors, etc.
- Is there any recent change in bowel habit or alteration of bowel habit?
- Have you seen blood or mucus in stool?
- Did you notice black tarry stool? (melena)
- Do you have pale stool with itching and dark urine? (obstructive jaundice)
- Do you have any mouth ulcer?

Genitourinary system:

- Do you have frequency of micturition?
- Are you passing larger amount of urine? (polyuria)
- Do you get up at night to pass urine? (nocturia)
- Do you feel pain during passing urine? (dysuria)
- If your bladder is full, do you have to void it immediately? (urgency)
- Do you notice narrow stream while passing urine? (poor stream)
- Does the flow stop on straining for micturition?
- Do you notice difficulty in starting micturition? (hesitancy)
- Is there any dribbling at the end of micturition? (terminal dribbling)
- Do you have incontinence of urine?
- What is the color of your urine? Is it mixed with blood? (hematuria)
- Do you have any loin pain? If any, does it go from loin to groin?
- Have you any problem with your sex life?
- Did you notice any ulcer, rash or lumps on your genitals?
- (In female) Do you have any discharge from your vagina or urethra?

Nervous system:

- Do you suffer from headache? If yes, ask details (see page …)
- Did you suffer from convulsion, fainting episodes, fits, blackout, vertigo or dizziness?
- Do you have problems with memory or concentration?
- Do you have trouble with your vision, hearing, taste or smell? Do you feel tinnitus?
- Do you have weakness (hemiplegia, paraplegia or monoplegia), tingling, numbness (pins and needles) or clumsiness in your arms or legs?
- Do you have tremor or any involuntary movement in any part of your body?
- Did you notice any problem with your balance?
- Did you ever have any head injury?

Locomotor system (musculoskeletal system):

- Do you have painful or stiff joints or swelling of joints? If yes, ask details (see page .....)
- Do you have backache or pain in the neck or muscular pain?
- Do you feel weak or have difficulty in standing up from sitting position or difficulty in raising hands above your head?

- Have you noticed any skin rash? (dermatomyositis)
- Have you ever had a dry mouth or mouth ulcer?
- Have your eyes been dry or red?

Hematological system:

- Do you have bleeding from anywhere? Or bruise easily?
- Have you noticed prolonged bleeding after a small cut?
- Have you noticed any lump under your armpit or in your neck or groin? (lymph nodes).
- Have you ever had blood clots in your legs or other parts of the body? DVT (deep venous thrombosis).
- Do you feel extreme weakness, dizziness, lassitude, dyspnea, palpitation? (anemia).
- Are you taking any drugs? Have you been exposed to chemicals or radiation? (aplastic anemia).

Endocrine system:

- Are you suffering from diabetes mellitus or do you have any thyroid problem?
- Have you noticed any neck swelling?
- Do you prefer hot or cold weather? Do you have excessive sweating? (cold intolerance indicates hypothyroidism, heat intolerance with excessive sweating indicates hyperthyroidism)
- Do you have tremor in your hands?
- Do you feel weak or fatigue?
- How is your appetite? (excessive appetite occurs in diabetes mellitus and thyrotoxicosis. Loss of appetite in malignancy, CKD, CLD, tuberculosis, hypothyroidism)
- Have you lost or gained weight? (weight gain in hypothyroidism, Cushing syndrome. Weight loss in hyperthyroidism, Addison's disease, diabetes mellitus). Also remember, a patient with a good appetite but weight loss is found in thyrotoxicosis and diabetes mellitus. Weight loss with poor appetite is because of malignancy, CKD, CLD, tuberculosis.
- Is there any change in your appearance, hair, skin or voice?
- Do you feel unusually thirsty? (excessive thirst may be because of diabetes mellitus, diabetes insipidus, hypercalcemia, psychogenic).

Reproductive system (in females):

- Did you have any miscarriage or abortion?
- During your past pregnancy, did you suffer from high blood pressure or diabetes mellitus?
- In your previous delivery (if any), did you suffer from prolonged bleeding?

Other questions in female patients:

- Do you feel any lump in your breast? If yes, ask – For how long do you have this lump? Is it getting larger? Is it painful or painless? Is it associated with any discharge, itching or skin change?

DESCRIPTION (OR ELABORATION) OF SYMPTOMS

(What else to know from patient's complaints or symptoms)

Once a patient complains of a symptom, you should ask certain important related questions regarding that symptom to determine the exact nature of the problem. You should also ask related questions in order to localize the disease to a system or organ of the body, understand the nature of the involvement (e.g. inflammatory, neoplastic) and find out the cause.

Usual symptoms related to anatomical systems of the body:

- General symptoms—fever, weight loss, weight gain, weakness, sleep pattern, malaise, itching, skin rash, excessive sweating.
- Gastrointestinal system—abdominal pain, nausea, vomiting, loss of appetite, heartburn, dysphagia, constipation, diarrhea, hematemesis, melena.
- Hepatobiliary system—jaundice, pain in the right hypochondrium, hematemesis, melena, abdominal distension (ascites), itching.
- Cardiovascular system—central chest pain, dyspnea, palpitation, cough, leg swelling, chorea, bluishness.
- Respiratory system—cough, chest pain, dyspnea, hemoptysis.
- Rheumatological system—arthritis, arthalgia, soft tissue swelling, bony deformity, skin rash, extra-articular features.
- Nervous system—headache, convulsion, weakness, vertigo, parsthesia, loss of consciousness, speech disturbance, memory disturbance, involuntary movements.
- Genitourinary system—dysuria, frequency, urgency, polyuria, retention, incontinence, loin pain, swelling of leg, puffiness of face, urethral discharge, impotence, premature ejaculation, infertility, abortion, miscarriage, menstrual irregularity, pelvic pain.
- Endocrine system—weight loss or gain, sweating, cold or heat intolerance, palpitation, tremor, pigmentation, polyuria, polydipsia.
- Dermatology—rash, itching, ulceration, blister, swelling or mass, pigmentation or depigmentation.
- Hematological system—prolonged bleeding, pallor, weakness, swelling over neck, axial or inguinal area.

Remember that different diseases involving different systems of the body may present with different symptoms. Here only the few common symptoms have been described:

- Fever
- Abdominal pain
- Chest pain
- Cough
- Dyspnea
- Vomiting
- Palpitation
- Jaundice
- Headache
- Joint pain
- Dysphagia
- Muscular weakness
- Weight loss
- Weight gain
- Vertigo
- Body swelling
- Cold or heat intolerance
- Polyuria
- Hematuria

If the patient complains of fever, ask:

What to be asked? See as follows:

- How long have you been suffering from fever?
- When does it start (morning, evening, night, etc.)? How long does it persist (few hours or throughout the day or night)? Is there any evening rise of temperature associated with night sweats?
- What was the highest recorded temperature?
- Is it associated with chills and rigors? Does it subside with sweating?
- Does it subside spontaneously or with antipyretic? If there is spontaneous remission, ask about the length of each episode of fever and the duration of the intervening afebrile period. However, if there is no spontaneous remission, ask if the temperature fluctuate more than 2ºC or not more than 1ºC? (to find whether the fever is continuous, remittent or intermittent).
- Is the fever punctuated by apyrexial period? (Undulant or Pel-Ebstein).
- Is the fever associated with skin rash or purpura?
- Is there any other associated symptom? (urinary complain, cough, chest pain, pain abdomen, headache, impaired or loss of consciousness, weight loss, polyarthritis).
- Is there any history of sexual exposure, homosexuality, travel abroad?
- Are you taking any drugs? (to exclude any drug fever).

Note Read the following features in relation to fever:

- Normal body temperature is 36.8ºC (mouth), 36.4ºC (axilla), 37.3ºC (rectum). Temperature > 37.3ºC in mouth or 37.7ºC in rectum is considered as fever.
- Temperature above 41.1ºC is called hyperthermia or hyperpyrexia. This may occur in severe infection, pontine hemorrhage, heat stroke, malignant hyperthermia, neuroleptic malignant syndrome, thyroid crisis, lobar pneumonia, datura poisoning.
- Hypothermia means temperature less than 35ºC.
- A recurrent bout of pyrexia followed by apyrexial period is called Pel-Ebstein fever. It is found in Hodgkin's disease (10% cases). This type of fever may be found in brucellosis (called undulant fever).
- Fever is of 3 types—intermittent, remittent and continued (other—hectic, Pel Ebstein).
- Intermittent: Fever that persists for several hours and always touches the baseline between attacks is called intermittent fever. It is of 3 types:
  a. Quotidian—It is characterized by paroxysm of fever that occurs daily (daily rise and fall). This type of fever may be found in tuberculosis, UTI, septicemia.
  b. Tertian—It is characterized by paroxysm of fever that occurs on alternate days. This may be found in benign tertian malaria (due to plasmodium vivax, rarely *P. ovale*).
  c. Quartan—It is characterized by paroxysm of fever that occurs with two days interval between consecutive attacks. This is found in quartan malaria due to *Plasmodium malariae* (rare).
- Remittent: If the fever fluctuates > 2ºC (3ºF) but does not touch the baseline, it is called remittent. This is found in any pyogenic infection (pyogenic liver abscess, acute bronchopneumonia, acute tonsillitis, septicemia, acute pyelonephritis), miliary tuberculosis, lymphoma.
- Continued: If the fluctuation of fever is not > 1ºC (1.5ºF) and the fever does not touch the baseline, it is called continued. This is found in typhoid, typhus, miliary tuberculosis, meningococcal meningitis, rheumatic fever, drug fever.
- Drug causing fever: A wide variety of drugs can cause drug fever. Common are—MAO inhibitor, tricyclic antidepressant, alpha-methyldopa, beta-lactam antibiotics, salicylate poisoning, LSD, ecstasy, procainamide, anticonvulsant, sulfonamide. Neuroleptic malignant syndrome may be caused by phenothiazine, butyrophenone, etc.
- Saddleback fever- Fever for few days, then no fever for one or two days followed by reappearance of fever. It occurs in dengue fever, Colorado tick fever, borreliosis, leptospira, yellow fever and influenza.
- Factitious fever: Sometimes patient purposefully show false rise of temperature. Usually found in young woman.

Contd...

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- Fall by crisis and lysis:
  a. When temperature subsides quickly to subnormal level, it is called fall by crisis. This may be found in lobar pneumonia, septicemic shock, enteric fever associated with perforation or bleeding.
  b. When temperature falls gradually over several days, it is called fall by lysis. This may be found in enteric fever, rheumatic fever, acute bronchopneumonia.
- Hectic temperature: It means sudden rise of very high temperature usually associated with chill and rigor, persist for few hours and then fall with profuse sweating. This may be found if pus is anywhere in the body, e.g. lung abscess, pyogenic liver abscess, empyema thoracis, subphrenic abscess, empyema of gallbladder, perinephric abscess, etc. Sometimes in septicemia or pyemia.
- Aseptic (non-infectious) fever: Fever without infection. May be found in SLE, lymphoma, leukemia, pontine hemorrhage, drug fever, early stage of acute myocardial infarction, heat stroke, thyrotoxic crisis, acute gout, excessive use of atropine injection (in OPC poisoning), etc.

Causes of fever in different diseases:

- Low grade fever with evening rise—tuberculosis.
- Fever with chill and rigor—acute pyelonephritis, acute cholangitis, subacute bacterial endocarditis, subphrenic abscess, pyogenic lung abscess, septicemia, lobar pneumonia, pyrogenic reaction after infusion or transfusion.
- Fever with chill and rigor that subsides with sweating—malaria.
- Fever with unconsciousness—cerebral malaria, meningitis, encephalitis, pontine hemorrhage.
- Fever with neck rigidity—meningitis, encephalitis.
- Fever with drenching night sweat—lymphoma, tuberculosis.
- Patient feeling feverish with excessive sweating—thyrotoxicosis.
- Pel-Ebstein fever (undulant fever)—Hodgkin's lymphoma.
- Fever with double rise (or triple rise)—Kala-azar.
- Step ladder pattern of fever—enteric fever.
- Relapsing fever—malaria, borreliosis, occasionally lymphoma (HD).
- Fever with myalgia—viral infection (e.g. influenza, dengue).
- Fever with skin rash (according to the day of appearance of rash)—Remember: "**V**ery **s**ick **p**erson **m**ust **t**ake **d**ouble **e**ggs."
  - 1st day—Varicella (chicken pox)
  - 2nd day—Scarlet fever
  - 3rd day—Pox (small pox)
  - 4th day—Measles, german measles (rubella)
  - 5th day—Typhus
  - 6th day—Dengue
  - 7th day—Enteric fever (rose spot)
  - Drug rash may appear anytime.

Note Other cause of skin rash with fever are infectious mononucleosis, Stevens Johnson syndrome, leptospirosis, Lyme disease, meningococcal septicemia, SLE, Still's disease, adult Still's disease, erythema nodosum, erythema multiforme, toxic shock syndrome, staphylococcal scalded skin syndrome, Sweet's syndrome, anthrax, etc.

- High temperature with pink maculopapular skin rash that disappears with the fall of temperature —Still's disease.
- Transient rise of temperature may occur due to a recent hot drink, hot bath, smoking, etc.
- Hyperpyrexia and rigidity in patient taking antipsychotic—neuroleptic malignant syndrome.
- Fever may be because of malignancy, such as hepatocellular carcinoma, bronchial carcinoma, renal cell carcinoma or because of drugs (drug fever).

Contd...

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- Fever with relative bradycardia: Normally, for 1°F rise in temperature, pulse increases by 10 beats per minute. If the rise of pulse rate is less than that, it is called relative bradycardia. It occurs in viral fever, 1st week of enteric fever, brucellosis, psittacosis, Weil's disease, etc.
- Fever with relative tachycardia: If rise in pulse rate is more than that is expected from increased temperature, it is called relative tachycardia. It occurs in acute rheumatic carditis, diphtheric myocarditis, severe tuberculosis, polyarteritis nodosa, etc.

If the patient complains pain, ask (formula- SOCRATES):

- **S**ite: Where is your pain?
- **O**nset: Was it gradual or sudden?
- **C**haracter: What is the nature of the pain? (dull ache, colicky, stabbing, compressive, crushing, agonizing, etc).
- **R**adiation: Does it radiate to anywhere?
- **A**ssociation (e.g. nausea, sweating, fever, skin rash).
- **T**iming of pain or duration: How long are you suffering from this pain? When does it come and how long does it persist?
- **E**xacerbating factor and relieving factor.
- **S**everity: How severe is it?

Note

Other questions will vary according to the site of pain, e.g. abdominal pain, chest pain, joint pain, etc. (see below).

Causes of pain in different diseases:

- Site: When localized to a part of the body, it gives a clue to the diagnosis. For example, pain in epigastrium may be because of peptic ulcer, cholecystitis, pancreatitis, etc. Central chest pain may be because of acute myocardial infarction, pericarditis, GERD, etc.
- Onset: May be sudden or gradual. Sudden onset usually indicates acute process. Gradual pain may occur in chronic cases.
- Character: Varies according to cause, e.g. peptic ulcer pain—hunger, boring or burning. Biliary or renal colic—severe, gripping, cramplike. Acute myocardial infarction—crushing, squeezing, compressing etc. Dissecting aneurysm—crushing or tearing. Pleuritic pain—sharp, stabbing. Tension headache—like a tight band around the head. Migraine—throbbing.
- Radiation—Pain may radiate to any part that will give a clue for specific diagnosis. For example, renal colic radiate from loin to groin, acute cholecystitis refer to right shoulder tip. Anginal pain may radiate to the inner aspect of left arm, neck and lower jaw.
- Duration—Pain lasting for seconds occurs in trigeminal neuralgia. Angina for 5 to 10 minutes, whereas pain of acute myocardial infarction last more than half an hour.
- Aggravating factor—Pleuritic pain is aggravated by coughing, change of posture, etc. Eating, exertion, activity, etc. aggravates anginal pain.
- Relieving factor—Rest relieves pain of angina pectoris. Food or drugs (like antacid) relieve duodenal ulcer pain. Rest in a dark room relieves migraine. Sitting up and leaning forward relieve pain of acute pancreatitis or pericarditis (Mohammedans prayer position). Lowering the arm relieves the pain of carpal tunnel syndrome. "Walking off" relieves the discomfort of restless leg syndrome.
- Severity—Very severe pain may be found in acute pancreatitis, biliary or renal colic, dissecting aneurysm, acute myocardial infarction, etc.

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- Associated factors: Excessive sweating, nausea, vomiting or sensation of impending death indicates acute myocardial infarction. Loin pain associated with temperature and hematuria indicates acute pyelonephritis. Premonitory symptoms (malaise and irritability followed by aura like fortification spectra) are common in migraine.

If the patient complains of abdominal pain, ask:

- **S**ite: What is the site of pain?
- **O**nset: Is it sudden or chronic? Does it disturb sleep at late night?
- **C**haracter: What is the character of pain?
- **R**adiation: Does it radiate to any site?
- **A**ssociation: Is it associated with diarrhea, vomiting, dyspepsia, altered bowel habit, urinary complaints, gynecological complaints, abdominal distension, etc.?
- **T**iming and duration – How long have you been suffering from this pain? When does it start? When does it go? Has it changed since it has begun?
- **E**xacerbating and relieving factors – What brings it on? What makes it worse? Is it related to meal? What makes it better?
- **S**everity—How severe is it?

Note Extra-abdominal cause or medical cause of abdominal pain:

- Diabetic ketoacidosis
- Henoch Schonlein purpura
- Addisonian crisis
- Acute intermittent porphyria
- Sickle cell crisis
- Hypercalcemic crisis (may be because of hyperparathyroidism)
- Polyarteritis nodosa
- Hyperlipidemia
- Hereditary angioedema (because of C1 esterase inhibitor deficiency)
- Paroxysmal nocturnal hemoglobinuria
- Chronic lead poisoning
- Familial Mediterranean fever
- Tabetic crisis in tabes dorsalis
- Others: Basal pneumonia (due to basal pleurisy), acute myocardial infarction (especially inferior wall infarction), Munchausen's syndrome, functional.

Causes of abdominal pain in different diseases according to site of pain:

- Epigastric pain: Peptic ulcer, acute pancreatitis, GERD, cholecystitis. (sometimes, there may be referred pain of acute myocardial infarction and basal pneumonia).
- Right iliac fossa pain: Acute appendicitis, Crohn's disease, salpingitis.
- Pain starts at mid abdomen and then shifts to right iliac fossa—Acute appendicitis.
- Left iliac fossa pain: Diverticulitis, volvulus, salpingitis, IBS.
- Right hypochondriac pain: Acute cholecystitis, liver abscess, acute viral hepatitis, enlarged tender liver in CCF, subphrenic abscess, perihepatitis (Fitz Hugh Curtis syndrome).
- Right hypochondriac colicky pain with jaundice: Gallstone in common bile duct.

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- Loin pain: Renal colic, acute pyelonephritis, perinephric abscess.
- Generalized abdominal pain: Peritonitis, inflammatory bowel disease, gastroenteritis.

Abdominal pain in different diseases according to onset:

- Acute pain: Acute cholecystitis, acute appendicitis, acute pancreatitis, intestinal obstruction, perforation of gas containing hollow viscus.
- Chronic pain: Peptic ulcer disease, irritable bowel syndrome.
- PUD may cause pain at late night.

Abdominal pain in different diseases according to severity and nature:

- Severe pain: Ureteric colic, acute pancreatitis, acute cholecystitis, burst appendicitis, perforation.
- Burning pain: Peptic ulcer disease.
- Colicky pain: Intestinal obstruction, ureteric stone, stone in common bile duct, ascariasis in common bile duct.

Abdominal pain in different diseases according to aggravating and relieving factors:

- Pain aggravated by smoking, alcohol, NSAIDs or steroid and relieved by antacids: Peptic ulcer disease. Duodenal ulcer is worse in empty stomach and relieved by taking food and gastric ulcer pain is worse after taking food.
- Pain aggravated by heavy meal and alcohol, but partially improved by bending forward: Acute pancreatitis.
- Pain aggravated by fatty food: Cholelithiasis.
- Pain aggravated by eating: Ischemic pain of gut.
- Pain aggravated by movement: Peritonitis.
- Pain relieved by vomiting: Gastric outlet obstruction.
- Pain relieved by spasmolytics or defecation: Intestinal obstruction.

Abdominal pain in different diseases according to radiation:

- Pain radiating to back: Acute pancreatitis, penetrating peptic ulcer.
- Pain radiating from loin to groin: Renal colic.
- Pain referred to right shoulder: Acute cholecystitis (because of diaphragmatic irritation), also diaphragmatic pleurisy.
- Pain referred to left shoulder: Splenic infarction, perisplenitis.
- Pain radiating to neck: Esophageal reflux.

If the patient complains of chest pain, ask:

- Site: Where is your pain? (central or peripheral part of the chest)
- Onset: How did the pain start? (sudden or gradual)
- Character: What is the nature of pain? (compressive, sharp, tearing, stabbing)
- Radiation: Does the pain radiate to any site?
- Timing (duration): How long does it persist?
- Exacerbating factors: What causes the pain? What makes it worse?
- Relieving factor: How the pain is relieved?
- Severity: How severe is it? (mild, moderate, severe)
- Associated features: Is there any other associated features?

Causes of chest pain in different diseases according to site and radiation:

- Central or retrosternal chest pain: Acute myocardial infarction, angina pectoris, pericarditis, myocarditis, dissecting aortic aneurysm, spontaneous pneumothorax, pulmonary embolism, reflux Esophagitis, Esophageal tear (Mallory Weis syndrome), mediastinitis, tracheitis, functional.
- Peripheral chest pain: Pleurisy, pneumonia, pneumothorax, pulmonary infarction, rib or chest wall involvement (injury, fracture or secondaries), costochondritis, herpes zoster, Bornholm disease.
- Pain radiating to inner part of left arm, neck or jaw occurs in IHD.

Chest pain in different diseases according to character:

- Compressing, crushing, constricting, squeezing or stabbing: Acute myocardial infarction.
- Sharp stabbing pain: Pleurisy or pericarditis.
- Burning pain: Gastroesophageal reflux disease (GERD).
- Discomfort or heaviness: Mediastinal compression due to tumor or lymphadenopathy.
- Atypical chest pain with no localization or no relation to coughing and breathing is psychogenic or due to anxiety.
- Very severe, tearing pain (sudden onset and radiates to back): Dissecting aortic aneurysm.

Chest pain in different diseases according to onset and duration:

- Sudden onset of pain: Acute MI, spontaneous pneumothorax, pulmonary embolism.
- Nocturnal chest pain: Heart failure, coronary artery spasm.
- Pain for less than 30 minutes: Angina pectoris.
- Pain for more than 30 minutes: Acute myocardial infarction.
- Long duration (weeks or months): Musculoskeletal, GIT disorder, cancer.

Chest pain in different diseases according to exacerbating and relieving factors:

- Pain on exertion, eating or emotion (3E) and relieved by rest or sublingual nitroglycerin: Angina pectoris.
- Pain precipitated by activity, persists for more than 30 minutes and is not relieved by rest or nitroglycerine: Acute myocardial infarction.
- Pain occurring after eating, lying flat, hot drinks or alcohol: Esophageal spasm or GERD.
- Unilateral sharp or stabbing pain aggravated by deep breathing, cough or change of posture: Pleuritic chest pain. This type of pain may also occur in chest wall disease (rib fracture, erosion, myalgia, etc.).
- Pain relieved by food: Duodenal ulcer.
- Pain relieved by sitting up and leaning forward: Pericarditis (not related to exertion).

Chest pain with other associated symptoms in different diseases:

- Pain with breathlessness: IHD, pulmonary embolism, pleurisy, anxiety.
- Pain with nausea, vomiting or sweating: Acute myocardial infarction.
- Pain with burning in chest or epigastrium: GERD.
- Sharp pain with cough: Pneumonia.
- Pain with difficulty in swallowing: Esophagitis, Esophageal carcinoma.
- Sudden pain (sharp and localized to a part of the chest) associated with severe dyspnea: Spontaneous pneumothorax.
- Central or retrosternal chest pain associated with repeated coughing: Tracheobronchitis.

Note If the pain is due to lesion in lung, pleura or chest wall, it is usually peripheral. Pain originating from centrally placed structure, such as heart, aorta, trachea, mediastinum, esophagus is usually central or retrosternal.

If the patient complains of cough, ask:

- How long have you been suffering from cough?
- Is it paroxysmal or persistent?

- Is it dry or productive?
- If productive of sputum, ask about its amount, color, odor, time of sputum production (morning), presence of blood and relation to posture change.
- Is it associated with hemoptysis? If yes, fresh or altered blood?
- Is it associated with chest pain, dyspnea?
- Is the cough aggravated by dust, cold air, smoke or pollen?
- Does it occur after eating or drinking?
- When does the cough get worse? (day or night).
- What is the character of cough?
- Are you taking any drug? (such as ACE inhibitor).
- Do you have diseases, such as rhinitis, asthma, heart disease, renal disorder?

Causes of cough in different diseases:

- Recent or acute onset: Respiratory infection, pneumonia, acute bronchitis.
- Chronic: COPD, bronchial asthma, bronchiectasis, ILD, tuberculosis.
- Occasional or paroxysmal cough: Bronchial asthma.
- Dry cough: ACE inhibitor (captopril, lisinopril), cough variant asthma, ILD, acute tracheobronchitis, tropical eosinophilia.
- Nocturnal cough: Bronchial asthma, LVF, tropical eosinophilia, post-nasal drip, aspiration.
- Cough with postural variation: Bronchiectasis, lung abscess, GERD.
- Painful cough or retrosternal pain: Tracheal involvement (tracheitis).
- Cough after eating or drinking: Esophageal reflux, tracheoesophageal Esophageal fistula.

Nature and character of cough indicate the following diagnosis:

- Croupy cough: Laryngitis (in children, diphtheria should be excluded).
- Harsh, barking, painful cough with stridor: Laryngeal disorder, such as laryngitis, tumor, etc.
- Barking cough: Acute epiglottitis.
- Loud and brassy cough: Pressure on trachea (by tumor).
- Hollow, bovine: Recurrent laryngeal nerve palsy (commonly due to bronchial carcinoma).
- Associated with whoop: Whooping cough.
- Cough with wheeze: Bronchial asthma, COPD.

Character of sputum may indicate the following diagnosis:

- Cough with profuse expectoration: Bronchiectasis, lung abscess, resolution stage of pneumonia.
- Yellowish or greenish or purulent sputum: Bronchiectasis, resolution stage of pneumonia.
- Foul smelling dark colored sputum: Lung abscess (usually with anaerobic infection).
- Rusty sputum: Pneumococcal pneumonia.
- Productive cough with frothy sputum occurs in pulmonary edema.

Sputum mixed with blood (hemoptysis):

- Respiratory cause: Bronchial carcinoma, pulmonary tuberculosis, pulmonary infarction, bronchiectasis.
- Cardiac cause: Mitral stenosis
- Blood dyscrasias: Hemophilia, Christmas disease, DIC, prolong use of anticoagulant, aspirin.

If the patient complains of dyspnea or difficulty in breathing, ask:

- Is the onset sudden (acute) or gradual (chronic)?
- Does it occur with exertion or at rest?
- If exertional, how much activity causes breathlessness? (Mild, moderate and severe. Ask how far he can walk or how many stairs he can climb or if he can undress himself without feeling breathlessness).

- Do you get breathless at night that wakes you up from sleep (PND)? How do you feel better?
- Do you feel breathless on lying flat? (orthopnea). How many pillows do you use at night?
- Is it paroxysmal or progressive?
- Is there any seasonal variation with breathlessness?
- Is there any history of recent travel abroad by air?
- Do you smoke? If yes, number of sticks per day.
- Is there any aggravating factor or occupational exposure to coal dust, silica, asbestos, animal dander?
- Is there any relieving factor? (drugs, rest, change of posture, after expectoration of sputum, etc).
- Is it associated with other symptoms? (cough, chest pain, wheeze or hemoptysis)?
- Is there any history of respiratory or cardiac disease or allergy or renal failure?

Note

Dyspnea may be defined as the subjective sensation of shortness of breath.

Causes of dyspnea in different diseases:

- Acute or sudden dyspnea—acute severe asthma, acute left ventricular failure (LVF), acute exacerbation of COPD, spontaneous pneumothorax, pulmonary embolism, ARDS, cardiac tamponade, acute laryngeal obstruction, diabetic ketoacidosis, conversion disorder.
- Chronic dyspnea—chronic bronchial asthma, COPD, DPLD.
- Dyspnea on mild exertion—COPD LVF.
- Orthopnea or PND—pulmonary edema (LVF, mitral stenosis).
- Dyspnea at rest—acute severe bronchial asthma, massive pneumothorax, ARDS, acute laryngeal edema, ILD (DPLD) in advanced stage, massive pulmonary embolism, cardiac cause (acute LVF), metabolic acidosis (diabetic ketoacidosis, lactic acidosis, salicylate poisoning, acute renal failure).
- Progressively increasing dyspnea—DPLD.
- Dyspnea with seasonal variation—bronchial asthma, chronic bronchitis.
- Dyspnea after air travel or immobilization – pulmonary embolism from DVT.
- Dyspnea aggravated by exposure to coal dust, silica, asbestos, animal dander—occupational asthma.
- Dyspnea may also be due to anxiety (or psychogenic) where the patient describes it to be an "inability to take a breath big enough to fill the lungs". The breathing is usually deep and punctuated with sighs.

Dyspnea with association:

- Dyspnea associated with wheezing—acute severe asthma, COPD, sometimes acute LVF, anaphylactic reaction.
- Dyspnea with stridor (indicates upper airway obstruction)—foreign body or tumor, acute epiglottitis, anaphylactic reaction, laryngeal trauma, laryngeal fracture.
- Dyspnea with crepitation—acute LVF (due to pulmonary edema), bilateral extensive bronchiectasis.
- Dyspnea but chest is clear—pulmonary embolism, metabolic acidosis (diabetic ketoacidosis, renal failure, lactic acidosis, salicylate poisoning), severe anemia, shock, pneumocystis jiroveci pneumonia, psychogenic.
- Dyspnea associated with unilateral chest pain—spontaneous pneumothorax.
- Dyspnea associated with shock—acute myocardial infarction.
- Dyspnea with high fever—pneumonia.

If the patient complains of vomiting, ask:

- How long have you been suffering from vomiting?
- How many times do you vomit a day?
- What are the contents of the vomitus?
- Does it contain blood (hematemesis)?
- What is the color of vomitus?
- Is it associated with nausea?
- Does it occur in the morning only?
- Do you induce vomiting?
- Is the vomiting projectile in nature?
- Does the vomiting relieve abdominal pain or discomfort?
- Is it associated with severe abdominal pain and absolute constipation followed by distension of abdomen?
- Is there any relation to food?
- Is there any history of head injury?
- Are you taking any drugs? Did you take radiation therapy?
- In female patient, ask about amenorrhea.
- Is it associated with chest pain, headache, tinnitus, vertigo, fever, jaundice, diarrhea weight loss?
- Ask about any other disease, such as hepatic, renal, migraine, carcinoma.

Note Non-gastrointestinal causes of vomiting – (A, B, C, D, E, F, G, H, I and P)

- **A**cute renal failure, Addison's disease
- **B**rain disease (raised ICP), Brainstem lesion
- **C**ardiac (acute myocardial infarction)
- **D**iabetic ketoacidosis
- **E**ar disease (labyrinthitis, Meniere's disease)
- **F**oreign substance (alcohol, drugs)
- **G**ravidity (hyperemesis gravidarum)
- **H**ypercalcemia
- **I**nfection (meningitis, encephalitis, appendicitis)
- **P**sychogenic.

Causes of vomiting in different diseases:

Contents of vomitus:

- Food taken on previous day (not stained with bile) indicates pyloric stenosis
- Bile stained contents indicate obstruction distal to the pylorus
- Fecal vomiting indicates distal small bowel obstruction, colonic obstruction or gastrocolic fistula
- Blood in vomitus indicates bleeding gastric ulcer, gastric erosion, carcinoma of stomach or ruptured esophageal varices.

Color of the vomitus:

- Coffee ground vomitus is because of conversion of hemoglobin to acid hematin by gastric acid. It indicates bleeding in the stomach.
- Bile stained (greenish) vomitus is because of obstruction distal to pylorus.

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Timing of vomiting:

- Early morning vomiting (before eating)—raised ICP, pregnancy, alcoholism
- Vomiting 1 hour after taking food—gastric outlet obstruction
- Vomiting occurring immediately after eating—psychogenic, peptic ulcer with pyloric spasm.

Vomiting with other associated features:

- Pregnancy is a common cause of vomiting (hyperemesis gravidarum)
- Vomiting without nausea—raised intracranial pressure (ICP)
- Projectile vomiting—gastric outlet obstruction
- Induced vomiting—gastric outlet obstruction and bulimia nervosa
- Pain abdomen relieved by vomiting—gastric outlet obstruction, gastric ulcer
- Vomiting with severe abdominal pain and absolute constipation—intestinal obstruction
- Acute vomiting with diarrhea and fever—infective gastroenteritis
- Vomiting with fever—inflammatory or infective origin (e.g. appendicitis)
- Vomiting with severe abdominal pain—renal or biliary colic
- Vomiting with jaundice—acute viral hepatitis
- Vomiting with chest pain—acute myocardial infarction
- Vomiting with unilateral headache—migraine, cluster headache
- Vomiting with tinnitus, vertigo—vestibular involvement
- Prolong history of vomiting with little or no weight loss—psychogenic.
- Vomiting may be because of many drugs, such as digoxin, opium, NSAIDs, chemotherapeutic drugs, aminophylline, etc. It may be because of radiotherapy as well.

If the patient complains of palpitation, ask:

- What do you really feel? (unexpected awareness of heartbeat)
- Did you check your pulse by yourself?
- How does it start? (spontaneous or with activity, anxiety, emotion, etc.)
- Is it paroxysmal or persistent?
- How long does it persist?
- How is it relieved?
- Have you ever missed a heartbeat?
- Do you get breathlessness, chest pain, dizziness or blackout with palpitation?

Note

Palpitation means sensation or abnormal awareness of heartbeat.

Causes of palpitation in various diseases:

- Sudden onset and termination of rapid, regular palpitation occurs in paroxysmal supraventricular tachycardia and atrial flutter with 2:1 block.
- Persistent palpitation may be because of anxiety neurosis, thyrotoxicosis, pregnancy, etc. Palpitation with anxiety occurs at night even.
- Sensation of a missed beat followed by a heavy beat occurs in premature atrial or ventricular contractions.
- Feeling of rapid palpitation followed by syncope indicates ventricular tachycardia.
- Rapid irregular palpitation indicates atrial fibrillation or flutter with variable block.
- Rapid regular palpitation indicates paroxysmal supraventricular tachycardia.
- Slow palpitation may be due to beta blocker or pulsus bigeminus.
- Other causes of palpitation are heart failure, ventricular tachycardia, AF, atrial flutter, etc.

If the patient complains of jaundice, ask:

- Did it start with anorexia, nausea and vomiting?
- Any history of contact with jaundiced patient or sexual exposure?
- What is the color of the stool? (yellowish, pale, dark)
- Do you have itching?
- Did you ever take any injection, infusion or blood transfusion? (HBV or HCV)
- Any history of IV drug abuse, tattooing or surgery? (HBV or HCV)
- Do you take alcohol or any drugs (look for hepatotoxic drugs)?
- Is there any family history of jaundice, consanguinity of marriage among parents?
- Did you suffer from recurrent jaundice?
- Any associated history of high fever, urinary complaints?
- Previous history of jaundice associated with any neurological abnormality?
- Have you traveled abroad?

Causes of jaundice in different diseases:

- Anorexia, nausea, vomiting—acute viral hepatitis, may be drug induced hepatitis.
- Itching with pale or dark pale stool—obstructive jaundice.
- Long standing jaundice with itching, pigmentation of skin—primary biliary cirrhosis.
- History of injection, infusion, blood or blood products transfusion, IV drug abuse and tattooing, homosexuality indicates probable infection with HBV or HCV.
- Family history of jaundice, consanguinity of marriage among parents and associated pallor indicates hereditary hemolytic anemia.
- Persistent mild jaundice indicates Gilbert's syndrome.
- Jaundice with high fever and urinary complain indicates leptospirosis.
- Recurrent jaundice with neurological abnormality—Wilson's disease.
- Jaundice with pregnancy—cholestatic jaundice of pregnancy.
- Painless progressive jaundice with palpable gallbladder—carcinoma of the head of the pancreas.
- Abdominal pain with fluctuating jaundice—bile duct stone or stricture, pancreatitis.

If the patient complains of headache, ask:

- What is the site of headache? (unilateral or diffuse, frontal, occipital or facial)
- What is the time of onset?
- How severe is it?
- What is the nature of headache? (throbbing, burning)
- How does it start?
- How long does it persist?
- Is it recurrent?
- Is there any aggravating factor, such as coughing, straining or change of posture?
- Is there any relieving factor?
- Is it preceded by any aura?
- Is it associated with fever, vomiting, weakness, blurring of vision, vertigo, nasal stuffiness, lacrimation, breathlessness?
- Are you taking any drug?
- Where have you been? (malaria endemic area)
- In female, ask about pregnancy (pre-eclampsia, especially if proteinuria and high blood pressure).

Note Worrying features or red flags in headache:

- First and worse headache—subarachnoid hemorrhage
- Thunderclap headache—subarachnoid hemorrhage
- Unilateral headache and eye pain—cluster headache, glaucoma
- Unilateral headache and ipsilateral symptoms—migraine, cerebral tumor, vascular headache
- Cough induced headache—raised ICP, cerebral venous sinus thrombosis
- Persistent unilateral headache with scalp tenderness over 50 years—temporal arteritis
- Headache with fever or neck stiffness—meningitis
- Changes in the pattern of usual headache—intracranial space occupying lesion, psychogenic
- Decreased level of consciousness—meningitis, encephalitis, cerebral malaria.

Causes of headache in different diseases:

Site of headache indicates:

- Unilateral headache preceded by flushing lights or zigzag lines—migraine.
- Headache over the occiput associated with neck stiffness—cervical spondylosis.
- Generalized headache, worse in the morning, associated with drowsiness and vomiting—raised intracranial pressure (ICP).
- Generalized headache with fever and photophobia and neck stiffness—meningitis.
- Persistent unilateral headache in temporal area—temporal arteritis (associated with temporal tenderness and blurring of vision).
- Pain on forehead, cheeks or behind the eyes—acute sinusitis.

Radiation of headache:

- Bilateral headache that extends to the top of the head, also unilateral headache radiating to neck with tenderness of neck muscles is suggestive of tension headache.
- Unilateral pain radiating to the throat, ear, eye, nose, cheeks, face is typical of neuralgia.

Time and mode of onset, severity and nature of headache:

- Headache at morning after waking up associated with vomiting—raised ICP
- Sudden, dramatic onset, severe headache associated with neck stiffness—subarachnoid hemorrhage
- Persistent headache for days or weeks—tension headache
- Persistent headache with scalp tenderness or tenderness over temporal artery—temporal arteritis
- Recurrent headache indicate migraine and cluster headache.

Duration of headache:

- Longer the history without progression is usually benign.
- Headache of migraine usually lasts less than 6 hours, but may persist for more than 24 hours.
- Episodes of cluster headache last less than an hour.
- In trigeminal neuralgia, each paroxysm last only seconds, recurring over several minutes.
- Tension headache may last for several days with or without disrupting sleep.

Nature of headache:

- Throbbing headache—migraine, cluster headache.
- Tight band-like around the head or pressure over the head—tension headache.
- Severe, thunderclap headache (like struck by a hammer)—subarachnoid hemorhage.
- Lancinating, paroxysmal pain indicates trigeminal neuralgia.

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Frequency and periodicity of headache:

- Sudden attack of pain in a repeated short burst with pain free interval lasting weeks or months are found in migraine, trigeminal neuralgia and cluster headache, angle closure glaucoma.
- Acute onset with rapid progression and continuous are found in meningitis and subarachnoid hemorrhage.
- Chronic daily headache—commonly due to cervical spondylosis, migraine, tension headache, drug (nitrates), chronic daily headache syndrome.

Special time of occurrence:

- Severe pain waking the patient from sleep in the early hours of morning is typical of cluster headache, also raised ICP.
- Pain precipitated by facial movement, such as eating, drinking, shaving, or brushing teeth are found in trigeminal or glossopharyngeal neuralgia.
- Pain in the jaw during chewing is typical of temporal arteritis.
- Headache at the onset of menarche and premenstrually is found in migraine.

Aggravating factor:

- Pain worse on coughing, bending, straining or posture change is due to raised ICP.
- Pain aggravated by hunger, intake of chocolate, cheese, alcohol or citrus fruit, contraceptive pill is suggestive of migraine.
- Idiopathic intracranial hypertension is associated with weight gain, use of corticosteroid, tetracycline, contraceptive pill, etc.

Relieving factor:

- Pain of migraine becomes less or improved in a dark place during acute attack, also improved or less severe during pregnancy.
- Rapid, dramatic response occurs in giant cell arteritis following steroid therapy.
- Headache usually responds to NSAIDs. But poor response occurs in tension headache.

Other disorders associated with headache:

- Headache with temporary visual loss or scintillating spots—migraine.
- Headache with nasal stuffiness or lacrimation—cluster headache.
- Headache with fever and neck stiffness—meningitis.
- Drug like nitrates may cause headache.
- Headache with fever and incoherent talk—cerebral malaria.

If the patient complains of joint pain, ask:

- Onset: Is it acute, gradual or chronic? Is it new or recurrent?
- Is there any history of trauma?
- How long are you suffering from joint pain?
- Is it associated with joint swelling?
- Which joints have been involved? Note the following:
  - Number of joints involved (mono, oligo or polyarthritis)
  - Symmetrical or asymmetrical.
  - Distribution of joint involvement (small or large joint involvement).
  - Upper or lower limb or both involvements.
- Does the pain move from one joint to other? (migratory or fleeting, additive)
- Does the pain worsen on activity or rest?
- Is there any morning stiffness? If present, how long does it persist? How does it subside? (improve with activity or exercise)

- Is it associated with redness, warmth and swelling? (suggest inflammation)
- Is there any deformity?
- Is there any extra-articular manifestation?
- Is this associated with dry mouth? (Sjogren syndrome)
- Do you have any skin or nail problem or is there any family history of such problem? (psoriatic arthritis)
- Is there any history of persistent bleeding?
- Is the arthritis preceded by urethritis, history of sexual contact, acute diarrhea (Reiter's syndrome, also may be eye problem)?
- Is there any history of frequent diarrhea? (IBD)
- Is there any history of tick bite in endemic area? (Lyme disease).

Note Remember the following points:

- Arthralgia means painful joint without swelling
- Arthritis means painful joint with swelling
- Seropositive means RA factor is positive (e.g. rheumatoid arthritis)
- Seronegative means RA factor is negative (e.g. ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, enteropathic arthritis)
- Monoarticular—single joint involved
- Oligoarticular or pauciarticular—2 to 4 joints involved
- Polyarticular—5 or more joints involved
- Migratory or fleeting—arthritis involving one joint then involving another
- Acute arthritis means < 6 weeks duration and chronic means > 6 weeks duration
- To remember, if any patient complains of arthritis—look for site or distribution of joint involvement, symmetry, joint swelling, deformity, movement, joint effusion, periarticular involvement, signs of inflammation (swelling, redness and warm), finally extra-articular manifestations
- Features of inflammatory arthritis are pain at rest, morning stiffness, joint inflammation and loss of function
- Non-inflammatory (mechanical) arthritis is more painful with activity and improves on rest.

Causes of joint pain in different diseases:

Monoarticular: (remember the formula – GRASP TH)

- **G**out, gonococcal arthritis
- **R**eactive arthritis
- **S**eptic arthritis
- **P**seudogout, psoriatic
- **T**ubercular
- **T**raumatic
- **H**emophilic (hemarthrosis)
- **A**ny polyarthritis may start as monoarthritis.

Polyarthritis:

- Rheumatic fever
- Rheumatoid arthritis (RA)
- Seronegative arthritis or spondyloarthropathy
- Osteoarthrosis (OA, commonly nodal OA)

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- Systemic lupus erythematisus (SLE)
- Gout, pseudogout
- Polymyalgia rheumatica.

Pattern of joint involvement:

- Distal interphalangeal joint (DIP) is involved in OA, psoriatic arthritis and gout
- Proximal interphalangeal joint (PIP) and metacarpophalangeal joints (MCP) are involved in rheumatoid arthritis
- First metatarsophalangeal (MTP) is involved in gout
- Sacroiliac (SI) joint is involved in ankylosing spondylitis
- Knee joint is involved in OA
- Bilateral symmetrical joint involvement— RA
- Asymmetrical joint involvement (also usually bigger joints)—seronegative arthritis
- Pain increased with activity, relieved by rest—mechanical arthritis
- Pain worse with rest, improved by activity—inflammatory arthritis
- Morning stiffness for more than 1 hour, relieved by activity indicates RA
- Fleeting arthritis—Rheumatic fever, gonococcal arthritis, others (SLE, Lyme arthritis, meningococcal arthritis, drug reaction or serum sickness, IBD, Whipple's disease).

Arthritis with deformity (deforming polyarthritis):

- Rheumatoid arthritis
- Seronegative spondyloarthropathy
- Chronic tophaceous gout
- Primary generalized osteoarthritis
- Infection – Lyme disease.

Note: In rheumatic fever, there is no deformity of the joint, "it licks the joint, kills the heart".

Extra-articular manifestations (when arthritis is associated with the following extra-articular findings, indicates the following diagnosis):

- Skin rash, oral ulcer—SLE
- Skin rash, heliotrope rash, muscular weakness—dermatomyositis
- Eye symptoms—RA, seronegative arthritis, SLE
- Dryness of mouth and eyes—Sjogren's syndrome
- Bowel symptoms—enteropathic arthritis (Crohn's disease, ulcerative colitis)
- Triad of urethritis, iritis and arthritis—Reiter's syndrome
- Psoriasis—psoriatic arthritis
- Renal stone—Gout, pseudogout
- Very high fever—septic arthritis
- Oral and genital ulcers, uveitis and skin lesion—Behcet's syndrome
- History of prolonged bleeding—hemophilic arthritis or Christmas disease
- History of sexual exposure indicates gonococcal or reactive arthritis
- History of tick bite indicates Lyme disease.

If the patient complains of dysphagia, ask:

- Can you show me with your finger at which level does the food get stuck?
- Is it due to solid or liquid or both?
- Is it painful or painless?
- Is it transient, intermittent or progressive?

- Do you have nasal regurgitation or cough during deglutition?
- Is it associated you heart burn or chest discomfort?
- Is there any difficulty to swallow?
- Did you notice bulging of the neck while eating or drinking?

Note Remember the following points:

- Dysphagia means difficulty in swallowing.
- Globus hystericus means feeling of a lump in the throat, without any organic cause. It does not interfere with swallowing and is not related to eating. It is found in conversion disorder (HCR).
- Odynophagia means painful swallowing. It is usually due to esophagitis. Causes are—esophageal ulceration due to candidiasis, herpes simplex infection, reflux esophagitis, corrosive poisoning, esophageal perforation.

Causes of dysphagia in different diseases:

According to nature of food:

- Difficulty more with solid food, less with liquid food—mechanical cause (because of esophageal stricture, tumor, pharyngeal web, esophagitis, dysmotility. Extrinsic compression on esophagus because of large retrosternal goiter, left atrial enlargement in MS, aortic aneurysm, posterior mediastinal mass.)
- Difficulty more with liquid, less with solid food—neurogenic cause, e.g. bulbar or pseudobulbar palsy (also called neurogenic dysphagia or motor dysphagia). It is associated with nasal regurgitation, choking or spluttering.
- Difficulty to both solid and liquid— indicates motility disorder (because of achalasia, diffuse esophageal spasm, pharyngeal causes, carcinoma esophagus, stricture of esophagus).

Association with pain:

- Painful dysphagia (odynophagia)—esophagitis (herpes simplex or candida), drug induced, ulceration, may be esophageal carcinoma, achalasia.
- Painless dysphagia—usually carcinoma of esophagus, achalasia or stricture.

According to site of obstruction:

- Lower retrosternal obstruction—carcinoma of esophagus, achalasia or stricture of esophagus.
- Obstruction at the level of cricoid cartilage—tumor, stricture, pharyngeal pouch.

According to duration or pattern:

- Transient dysphagia—esophageal infection.
- Progressive dysphagia—carcinoma, achalasia or stricture.
- Intermittent dysphagia or if present only with first few swallows of food—esophageal spasm or esophageal ring.

Dysphagia with other symptoms:

- Dysphagia with nasal regurgitation or dysphonia or choking on trying to swallow—suggestive of pharyngeal causes of dysphagia that are due to bulbar or pseudobulbar palsy. Also, left recurrent nerve palsy due to mitral stenosis (Ortner syndrome).
- Dysphagia with chest discomfort and heart burn—hiatus hernia, GERD, diffuses esophageal spasm.
- Dysphagia with nocturnal cough and dyspnea—GERD, achalasia.
- Neck bulge or gurgle during drinking—pharyngeal pouch.
- Dysphagia with anemia and koilonychia—Plummer Vinson syndrome (iron deficiency anemia).
- Dysphagia with palmar hyperkeratosis—tylosis.

If the patient complains of muscular weakness, ask:

- Is it generalized or localized?
- Distribution: Is it proximal or distal?
- Onset: Is it sudden or gradual?
- Progression: Is it ascending or descending?
- Does it worsen or improve with activity?
- Is there other features, such as muscle pain, skin rash, sensory loss, loss of bowel or bladder control?
- Do you take any drug or alcohol?

Note Remember the following points:

- Myopathy is associated with proximal muscular weakness, except myotonia dystrophica that involves distal muscles.
- Neuropathy is associated with distal muscular weakness, except diabetic amyotrophy (that involves the proximal muscles).

Causes of muscular weakness in different diseases:

Group of muscles involved:

- Generalized: Hypokalemia, hyperkalemia, malnutrition, chronic illness.
- Localized: Usually neurological (hemiplegia, paraplegia, monoplegia).
- Proximal weakness: All myopathy (except myotonia dystrophica that causes distal weakness)—dermatomyositis or polymyositis, myasthenia gravis, myasthenic myopathic syndrome (Eaton-Lambert syndrome), Cushing's syndrome, diabetic amyotrophy, thyrotoxicosis (also hypothyroidism), polymyalgia rheumatica, osteomalacia, hyperparathyroidism, periodic paralysis, alcohol and drugs, McArdle's syndrome (myophosphorylase deficiency, there is stiffness and cramps of muscle after exercise, that is hard and painful on movement).
- Distal weakness: Peripheral neuropathy, myotonia dystrophica, Charcot-Marie-tooth disease.

Onset and progression:

- Sudden onset, generalized weakness: Hypokalemic periodic paralysis, thyrotoxic periodic paralysis.
- Sudden onset, localized weakness: Stroke (usually hemiparesis), spinal cord compression (usually paraparesis).
- Weakness that progress over hours to days: GBS, spinal cord lesion.
- Gradual onset and slowly progressive weakness: Peripheral neuropathy, spinal cord lesion, motor neuron disease, myasthenia gravis, myopathy.
- Weakness worsens with activity: Myasthenia gravis.
- Weakness improves with activity: Eaton Lambert syndrome.
- Weakness worsen on exposure to heat (e.g. hot bath): Multiple sclerosis.
- Sudden ascending paralysis occurs in GBS.

Weakness with associated symptoms:

- Weakness with skin rash: Dermatomyositis.
- Weakness associated with muscle pain: Polymyalgia rheumatica, polymyositis or dermatomyositis, hypothyroidism (Hoffman's syndrome), diabetic myopathy, hypoparathyroidism.
- If there is fasciculation: Indicates lesion involving the anterior horn cell or root (in motor neuron disease).
- Drugs causing muscular weakness: Statins, steroids, chloroquine, zidovudine, vincristine, alcohol, cocaine.

- Weakness with preserved reflex: Myotonia dystrophica, also myasthenia.
- Weakness with loss of reflex: Neuropathy, also in case of myopathy, lower motor neuron lesion.
- Weakness with exaggerated reflex: Upper motor neuron lesion (MND, typically in amyotrophic lateral sclerosis).

If the patient complains of weight loss, ask:

- How much weight did you lose? Over what period?
- How is your appetite?
- How is your bowel habit? (If frequent diarrhea or loose motion, ask details regarding color, amount, presence of blood, etc.).
- Do you feel excessively thirsty and micturate frequently?
- Do you have other symptoms, such as cough, fever, night sweat?
- Do you have palpitation?
- Do you prefer hot or cold environment?
- Do you feel that you are getting darker than before? (any change in your complexion?)
- Do you have vomiting? If yes, is it spontaneous or induced?
- Do you take alcohol or any other substance?

Note Also remember the following points:

- A detailed systematic enquiry should be made to find out any malignancy.
- History regarding intravenous drug intake, blood or blood product transfusion, extramarital sexual contact, traveling abroad and other high-risk behavior for HIV infection should be sought.
- Weight loss means reduction of 5% of body weight or 5 kg within 6 months is considered significant.
- Weight loss may be physiological because of dieting, exercise, starvation or less intake in old age.

Causes of weight loss in different diseases:

- Weight loss with low grade evening fever, cough and night sweats indicates tuberculosis.
- Weight loss in spite of good appetite or high food intake—thyrotoxicosis or diabetes mellitus. Also, may be in malabsorption syndrome or bulimia (binge eating).
- Weight loss with heat intolerance, diarrhea, palpitation, etc.—thyrotoxicosis.
- Weight loss with polyphagia, polyuria and polydipsia (3P)—diabetes mellitus.
- Weight loss with diarrhea or steatorrhea indicates malabsorption syndrome.
- Weight loss with pigmentation and hypotension—Addison's disease.
- Extreme cachexia in young female with history of diet control, heavy exercise, induced vomiting and amenorrhea – anorexia nervosa.
- Any malignancy, chronic debilitating illness like cardiac, pulmonary or renal failure or malnutrition may cause weight loss.
- HIV infection should be ruled out.

If the patient complains of weight gain, ask:

- How much weight did you gain? Over what period?
- How is your appetite?
- Do you feel weak or fatigue?
- How is your bowel habit?

- Do you prefer hot or cold environment?
- Do you take any drugs or alcohol?
- How is your menstrual cycle? Any growth of excessive hair? (For female).
- Do you have headache?

Causes of weight gain in different diseases:

- Weight gain with loss of appetite indicates hypothyroidism (other features of hypothyroidism are cold intolerance, fatigul and constipation.
- Weight gain with increased appetite—Cushing's syndrome, hypoglycemia (occurs in insulinoma), hypothalamic disease.
- Weight gain with central obesity indicates Cushing syndrome (other features of Cushing syndrome are moon face, plethora, hypertension, easy bruising, etc. The most common cause is prolong use of steroid). Drugs, such as corticosteroid, TCA, sulfonylurea, beta blocker, estrogen containing OCP may cause weight gain.
- Young obese female patient with irregular cycle or amenorrhea and hirsutism indicates polycystic ovarian syndrome.
- Headache indicates pituitary cause of weight gain.
- If only weight gain with more food intake without any other complain—simple obesity. Also, may be familial.
- Some congenital anomalies may cause weight gain, such as Prader Willi syndrome, Laurence Moon Biedl syndrome, Klinefelter syndrome, Kallman syndrome, Noonan syndrome.

If the patient complains of vertigo, ask:

- Onset—is it sudden or gradual?
- Is it recurrent, persistent or progressively increasing?
- If recurrent, what is the frequency and duration?
- Do you feel that the surrounding is moving or do you feel yourself to be moving?
- What causes the vertigo? (movement of the head, standing from sitting position, traveling in a motor vehicle, anxiety, stress, menstruation, etc.).
- Does it relate to change in head posture?
- How severe is it?
- Did you ever suffer any head injury or trauma to the head?
- Is it associated with symptoms, such as hearing loss, tinnitus, headache, nausea, vomiting, pallor, sweating, double vision, frequent fall, ataxia, focal weakness, confusion or loss of taste sensation?
- Do you take any drugs? (aminoglycoside).

Note Remember the following points:

- **Dizziness:** It means a sensation of faintness, light-headedness, spinning or giddiness. But the term may be used by the patient to describe other inappropriate sensations, such as confusion, blurring of vision, tingling, etc. Even the sensation of ataxia is sometimes described as dizziness. Causes of recurrent dizzy spells over 65 years of age are—postural hypotension, vertebrobasilar insufficiency or cerebrovascular disease, arrhythmia, hyperventilation due to acute anxiety or panic attack.
- **Syncope:** It means transient loss of consciousness due to reduction in cerebral blood flow.
- **Vertigo:** It is a sense of unsteadiness and loss of balance with a feeling of rotation of the body or environment, due to impaired vestibular function of either central or peripheral origin.

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- **Drop attack:** Sudden fall to the ground while walking or standing with transient loss of consciousness. The patient does not remember the actual fall. It is common in middle age or elderly woman. It is due to vertebrobasilar TIA, but no evidence of vascular disease.
- Vertigo may be due to **central lesion** (brainstem or cerebellum) or **peripheral lesion** (labyrinthine lesion).
- **Peripheral vertigo** is usually sudden in onset, severe in nature, unilateral, lasting for few seconds or few days and often recurrent. It is usually associated with unilateral deafness or tinnitus. There may be ear pain or discharge. There may be unidirectional nystagmus with slow phase toward the affected side and fast component toward the opposite side. Common cause is labyrinthine disorder.
- **Central vertigo** is usually chronic and mild, often bidirectional and associated with other central abnormalities. Patient with central vertigo cannot stand or walk. Direction of fall is variable. Vertical nystagmus (up or down beat) is pathognomonic of central vertigo (brainstem lesion). Central vertigo is commonly because of vascular insufficiency of brainstem or basilar artery insufficiency supplying cerebellum.
- **Vertigo due to vascular cause** (vertebrobasilar insufficiency) occurs in elderly and is usually associated with hypertension, CVA, IHD, smoking, diabetes mellitus and dyslipidemia.
- **Common causes of vertigo:**
  - Central vertigo—brainstem ischemia or infarction, migraine, multiple sclerosis.
  - Peripheral vertigo—Meniere's disease, benign positional vertigo, vestibular neuronitis, drugs (gentamicin, anticonvulsant), trauma.

Causes of vertigo in different diseases:

- Acute or sudden vertigo—vestibular neuronitis, labyrinthitis, multiple sclerosis, skull fracture, Meniere's disease, CVD involving brainstem or cerebellum.
- Recurrent vertigo lasting less than a minute—benign positional vertigo, post-traumatic vertigo, psychogenic.
- Recurrent vertigo lasting for minutes to hours—migraine, vertebrobasilar insufficiency, Meniere's disease.
- Spontaneous attack of prolong vertigo for a day or more—labyrinthitis, multiple sclerosis, brainstem infarction.
- Vertigo with hearing loss and tinnitus indicates peripheral disorder, e.g. Meniere's disease, labyrinthitis. This may be due to ototoxic drugs like aminoglycoside.
- Vertigo associated with neurological disorders or chronic vertigo without any cochlear symptom suggests a central lesion, e.g. lesion in brainstem, cerebellum, CP , etc.
- Vertigo precipitated by movement of the head in a specific direction—benign positional vertigo.
- Vertigo with slowly progressive unilateral hearing loss, tinnitus, dizziness and disequilibrium—acoustic neuroma.
- Intermittent brief vertigo with occasional drop attack, ataxia, visual loss, double vision and confusion—vertebrobasilar insufficiency.
- Episodic, recurrent vertigo with auditory symptoms, headache, photophobia, aura—migraine.
- Vertigo with facial weakness and loss of taste sensation—Ramsay Hunt syndrome.
- Triad of episodic vertigo, tinnitus and progressive deafness—Meniere's disease.
- Psychogenic vertigo is usually associated with agoraphobia (fear of large open space or crowd). It differs from organic vertigo in which, despite discomfort, patient attempts to work. Also, there is no nystagmus in psychogenic vertigo (nystagmus is usually present in organic disease).

If the patient complains of swelling of the body, ask:

- Is it generalized, involving the whole body or localized to a part?
- If generalized, where did it first appear? (Face, feet, abdomen).

- If localized, is the swelling painful?
- What is the amount of urine you pass everyday? Is there any pain or burning?
- What is the color of your urine?
- Do you feel palpitation, cough, chest pain or breathlessness on exertion?
- Any history of sore throat or skin infection?
- Do you have diabetes mellitus or hypertension?
- Do you have cold intolerance, constipation, lethargy?
- Do you take any drugs? (steroid, amlodipine, nifedipine).
- How is your bowel habit?

Note Remember the following points:

- Generalized edema indicates hypoalbuminemia (because of less intake, nephrotic syndrome, CLD, malabsorption, etc.) or fluid overload (CCF, glomerulonephritis, etc.).
- Localized edema indicates venous (DVT) or lymphatic obstruction (lymphedema, allergic) or inflammatory (cellulitis).

Causes of body swelling in different diseases:

Generalized swelling:

- Generalized swelling starting at the face (especially periorbital puffiness mostly at the morning) with oliguria indicates a renal cause (glomerulonephritis or nephrotic syndrome). If history of skin or throat infection, followed by smoky or cloudy urine, it indicates post streptococcal glomerulonephritis.
- Generalized swelling with anemia in a hypertensive patient indicates CRF.
- Swelling starting at the legs, ascending upwards and exertional dyspnea indicates cardiac cause, commonly CCF.
- Gradual swelling of whole body with non-pitting edema, cold intolerance, lethargy—hypothyroidism.
- Generalized swelling may also occur in wet beri beri, also in cyclical edema.
- Swelling with steatorrhea indicates hypoalbuminemia due to malabsorption.

Abdominal swelling:

- In CLD (cirrhosis of liver), abdominal swelling (ascites) starts first.
- Abdominal swelling associated with pain in abdomen, anorexia and weight loss indicates abdominal malignancy with metastasis in the peritoneum.
- In constrictive pericarditis, abdominal swelling occurs first, followed by swelling of the leg in advanced stage.

Localized swelling:

- Unilateral leg swelling with non-pitting edema (lymphedema in filariasis).
- Unilateral painful leg swelling of sudden onset—DVT.
- Pitting unilateral lower limb edema may be due to DVT, compression of large veins by tumor or lymph nodes.
- Non pitting lower limb edema may be due to hypothyroidism or lymphedema (filariasis, malignancy, congenital, allergic or Milroy's disease).
- Localized swelling—angioedema.
- Unilateral painful and red swelling in a limb with fever in a toxic patient—cellulitis.
- Gradual truncal swelling in a patient taking steroid—Cushing's syndrome.
- Drugs causing pedal edema—nifedipine, amlodipine.
- Unilateral edema of the arm may occur following surgery or removal of axillary lymph node (in breast carcinoma).

If patient complains excessive cold or heat intolerance, ask:

- If the patient has cold intolerance ask, features of hypothyroid, such as weight gain, lethargy, increased sleepiness, constipation, etc.
- If patient has heat intolerance or excessive sweating, ask to exclude thyrotoxicosis, e.g. increased appetite, weight loss, palpitation, diarrhea, irritability.

Causes of heat or cold intolerance in different diseases:

- Causes of cold intolerance are hypothyroidism, old age, excessive environmental cold.
- Causes of heat intolerance are thyrotoxicosis, menopausal syndrome.
- Excess sweating is called hyperhidrosis. Causes are—anxiety neurosis, thyrotoxicosis, pheochromocytoma, acromegaly, autonomic neuropathy (gustatory hyperhidrosis), excess use of antipyretic, exposure to hot environment, fever, severe pain, menopausal syndrome, malignancy, amyloidosis, neuroleptic malignant syndrome, cholinergic or parasympathomimetic drug side effect, drugs, such as thyroxin, somatostatin analog, vasopressin, epinephrine, withdrawal of drugs like gabapentin or opiate.
- Less or no sweating is called anhidrosis. Causes are—hypothyroidism, hypothermia, autonomic neuropathy, Sjogren's syndrome, anticholinergic drug therapy, vitamin A deficiency, hypoadrenalism.

If patient complains of polyuria, ask:

- What is the amount of water you take and void everyday?
- Are you suffering from diabetes mellitus?
- Is it associated with excessive thirst?
- Do you have excessive thirst with polyphagia?
- Are you taking any drugs? (diuretic, lithium, analgesic, cidofovir, foscarnet)
- Do you take alcohol or excessive coffee?
- Do you have excess thirst, abdominal pain, constipation, etc.?
- Do you have history of head trauma, pituitary surgery or stroke?
- (Take history of psychiatric illness).

Note Remember the following points:

- **Polyuria** means passage of large volume of urine, usually more than 3 L per day in the absence of excess intake of water. Causes are—diabetes mellitus, diabetes insipidus (cranial and nephrogenic), psychogenic polydipsia, hypercalcemia due to any cause, CRF, excessive intake of water, drugs (diuretic, alcohol), renal tubular disease, adrenal insufficiency.
- **Anuria** means urine output less than 50 mL per day. The patient may not pass urine at all.
- **Oliguria** means passage of less than 400 mL urine daily.
- **Nocturia** means the need to get up during night to pass urine.
- **Normal** urine output is 800 to 2500 mL per day in temperate climate.
- **Frequency** of micturition means frequent passage of small amounts of urine (not increased volume). Causes are—urethritis, cystitis, enlarged prostate, bladder neoplasm, pregnancy.
- **Urgency:** It means immediate desire to pass urine.
- **Hesitancy:** It is defined as difficulty in initiating the process of micturition.
- **Dysuria:** It is a specific form of discomfort arising from the urinary tract, in which there is pain immediately before, during or immediately after micturition.

Causes of polyuria in different diseases:

- Polyuria associated with polyphagia and polydipsia is highly suggestive of diabetes mellitus (may be also in thyrotoxicosis, obesity and bulimia).
- Polyuria with excessive thirst—diabetes insipidus, anxiety, also diabetes mellitus.
- History of head injury or surgery suggests cranial diabetes insipidus.
- Polyuria with constipation, abdominal pain and excess thirst indicates hypercalcemia.
- History of psychiatric disease indicates psychogenic polydipsia.
- Drugs causing polyuria—diuretic, lithium, analgesic, cidofovir, foscarnet, etc.

If the patient complains of hematuria, ask:

- Is it at the beginning of micturition or at the end or throughout? (initial, terminal or total)
- Do you feel pain or burning during micturition? (dysuria)
- Is this associated with frequency, urgency or hesitancy?
- Do you have loin pain? Does it radiate to the groin? Do you have pain in lower abdomen or generalized abdominal pain? (If the patient complains of any pain, take detailed history as given in page …).
- Have you noticed bleeding from any other part of the body?
- Do you have fever? (If yes, take detailed history of fever).
- Is it associated with nausea or vomiting?
- Have you noticed any rash? Is it associated with joint pain and swelling?
- Do you take any drugs? (anticoagulant, antiplatelet, analgesic, cyclophosphamide, antibiotic).
- Did you ever pass stones previously?
- Did you suffer from any kind of trauma?
- Did you suffer from skin infection or sore throat recently?
- Do you have hypertension, exertional breathlessness and swelling of the body?
- Is there any history of renal disease in your family?
- In female, enquire whether she is menstruating.
- Take occupational history specially looking for exposure to radiation or industrial chemicals like benzene.
- Have you recently traveled to any Middle Eastern country (to exclude bilharziasis or schistosomiasis)?

Note Remember the following points:

- Causes of high colored or dark or red urine are—hematuria, hemoglobinuria, myoglobinuria, porphyria and deep jaundice. Also, drugs like rifampicin, phenolphthelein, clofazimine, phenindione and some food like beet root, senna, rhubarb, and blackberry.
- Hematuria is the presence of fresh blood (intact RBC) in urine.
- Presence of hemoglobin in urine is called hemoglobinuria (no RBC). It indicates intravascular hemolysis.
- Loss of muscle pigment in urine is called myoglobinuria (no RBC in urine microscopy). This is found in rhabdomyolysis.
- Presence of porphobilinogen in urine is found porphyria. Here the urine is normal in color when it is voided but becomes dark (Burgundy-wine) on standing for few hours. It is detected by Ehrlich's aldehyde test. This type of urine may be found in alkaptonuria. It is due to presence of homogentisic acid in urine.
- Blood appearing at the beginning of micturition indicates a lower urinary tract cause (urethra). Uniform blood staining throughout the stream points to a cause higher up (bladder and above). Terminal hematuria indicates severe bladder irritation by stone or infection or neoplasm, also disease of prostate.

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- Hematuria may be detected by dipstick. False positive may occur in hemoglobinuria, myoglobinuria, beet root, porphyria, alkaptonuria, rifampicin, phenindione, phenolphthalein.
- Presence of red cell cast in urine indicates bleeding from kidney, usually glomerulonephritis.
- Macroscopic hematuria is more likely due to tumors of renal tract. Sometimes, it may be found in severe infection and renal infarction.

Causes of hematuria in different diseases:

- Hematuria with dysuria indicates cystitis or urethritis (UTI).
- Hematuria with more than trace of protein in urine suggests that the blood is of renal origin.
- Hematuria with loin pain, high grade fever with chill and rigor, nausea or vomiting indicates acute pyelonephritis.
- Hematuria with fever may also be found in infective endocarditis with renal involvement, collagen vascular disease (SLE).
- Hematuria with loin to groin pain indicates renal stone. If stone in urinary bladder, there may be pain in lower abdomen.
- Painful hematuria may be found in loin pain hematuria syndrome.
- Hematuria either painful or painless may be found in UTI, adult polycystic kidney disease, reflux nephropathy and renal scarring, renal stone without obstruction.
- Painless hematuria may be due to tumor of kidney, ureter, bladder and prostate, renal tuberculosis, glomerulonephritis, schistosomiasis (bilharziasis), bleeding disorders, benign enlargement of prostate, IgA nephropathy, infective endocarditis, hypertensive nephrosclerosis, interstitial nephritis, drugs like heparin and oral anticoagulant.
- Bilharziasis should be strongly suspected in any patient who has been to Middle East recently.
- Hematuria with obstructive features in elderly male indicates benign enlargement of prostate or carcinoma of prostate.
- Hematuria with previous history of skin infection or sore throat, hypertension and generalized body swelling indicates acute glomerulonephritis.
- Hematuria due to drugs—analgesic (papillary necrosis or analgesic nephropathy), cyclophosphamide (haemorrhagic cystitis), antibiotic (interstitial nephritis), anticoagulant, antiplatelet.
- Hematuria with hypertension—renovascular disease..
- There may be family history of renal disease in patient with polycystic kidney disease.
- Bleeding from multiple sources indicates bleeding disorder, also may be drug induced.
- Hematuria with bruise or purpura may be due to coagulation disorder, Henoch Schonlein purpura or vasculitis.
- Hematuria with abdominal pain and vasculitic rash over lower limbs indicate Henoch Schonlein purpura.
- In young fit athlete, hematuria may be due to exercise induced hematuria.
- Hematuria associated with diabetes mellitus or sickle cell disease or trait—papillary necrosis.

CHAPTER 2

Respiratory System

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BRONCHIAL ASTHMA

CHIEF COMPLAINTS

- Difficulty in breathing for … years
- Cough for … months
- Wheeze and tightness in the chest … months.

HISTORY

History of present illness: According to the statement of the patient, he has been suffering from difficulty in breathing for the last … years. Initially, for a few years, it was episodic, occurring mainly during the winter seasons, and he was asymptomatic in between the attacks. But for the last … years, it is persistent with occasional exacerbations. His breathlessness is worse at night and sometimes during the daytime. It is aggravated by cold, dust and activity. There is no history of orthopnea or paroxysmal nocturnal dyspnea.

The patient also complains of cough which is usually dry, with occasional scanty mucoid sputum expectoration, but no history of hemoptysis. Cough is present throughout the day and night, more on exposure to dust or cold. He also experiences wheeze and tightness of the chest during coughing. For severe attack of breathlessness and cough, he was hospitalized twice within the last ... months.

On query, the patient agreed that he has occasional attack of running nose and sneezing, more marked on exposure to dust. There is no history of chest pain, weight loss or fever. His bowel and bladder habits are normal.

History of past illness: He is non-hypertensive, no history suggestive of cardiac illness or reflux esophagitis.

Family history: His brother is suffering from bronchial asthma and food allergy.

Personal history: He is a school teacher, smokes 10 to 15 cigarettes daily for the last 10 years. There is no history of exposure to cotton, coal, etc.

Drug history: He uses bronchodilator and steroid inhalers, and used to take tablets like aminophylline, ketotifen and montelukast.

GENERAL EXAMINATION

- The patient is dyspneic
- Decubitus is propped up
- No anemia, jaundice, cyanosis, edema, clubbing, koilonychia or leukonychia
- No lymphadenopathy or thyromegaly
- Neck vein: Not engorged
- Purse lip: Absent
- Nasal polyp: Present on both sides
- Pulse: 120/min
- BP: 120/70 mm Hg
- Respiratory rate: 24/min.

SYSTEMIC EXAMINATION

Respiratory System

Inspection:

- Shape of the chest—Normal
- There is indrawing of intercostal spaces, suprasternal and supraclavicular excavation and prominent accessory muscles of respiration.

Palpation:

- Trachea: Central. Tracheal tug absent
- Apex beat: In the left 5th intercostal space in midclavicular line, 8 cm from midsternal line, normal in character
- Chest expansion: Reduced
- Vocal fremitus: Normal.

Percussion:

- Percussion note: hyperresonance in both sides
- Area of liver dullness: In 5th ICS in the right midclavicular line
- Area of cardiac dullness: Normal.

Auscultation:

- Breath sound: Vesicular with prolonged expiration
- Vocal resonance: Normal
- Added sounds: High pitched rhonchi are present in both sides of the chest, more marked on expiration.

FET (forced expiratory time): > 6 seconds (normally <6 seconds).

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 50 years old, school teacher, normotensive, nondiabetic, hailing from …, presented with difficulty in breathing, cough, wheeze and tightness of the chest for the last … years. Initially, for few years, it was episodic, occurring mainly during the winter seasons, and he was asymptomatic in between the attacks. But for the last … years, it is persistent with occasional exacerbations. His breathlessness is worse at night and sometimes during the daytime. It is aggravated by cold, dust and activity. There is no history of orthopnea or paroxysmal nocturnal dyspnea. The patient also complains of cough which is usually dry, with occasional scanty mucoid sputum expectoration, but no history of hemoptysis. Cough is present throughout the day and night, more on exposure to dust or cold. He also experiences wheeze and tightness of the chest during coughing. For severe attack of breathlessness and cough, he was hospitalized twice within the last ... months. On query, the patient agreed that he has occasional attack of running nose and sneezing, most marked on exposure to dust. There is no history of chest pain, weight loss or fever. His bowel and bladder habits are normal. There is no history suggestive of cardiac illness or reflux oesophagitis. His brother is suffering from bronchial asthma and food allergy. He smokes 10 to 15 cigarettes daily for the last 10 years. There is no history of exposure to cotton, coal, etc. He uses bronchodilator and steroid inhalers, and used to take tablets like aminophylline, ketotifen and montelukast.

On examination, general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is chronic bronchial asthma.

Q. What is your **differential diagnosis**?

A. COPD (Chronic obstructive pulmanary disease).

Q. Why not **chronic bronchitis**?

A. In chronic bronchitis, there is presence of cough with sputum production not attributable to other causes, on most of the days for at least 3 consecutive months in a year for at least 2 successive years.

Q. Why not **cardiac asthma**?

A. Cardiac asthma means left ventricular failure in which the patient usually presents with sudden severe dyspnea and cough with profuse mucoid expectoration. On examination, there are bilateral basal crepitations and no rhonchi or wheeze.

Q. What **investigations** do you want to do in bronchial asthma?

A. As follows:

1. Full blood count.
2. X-ray chest of PA view.
3. Sputum for eosinophil count.
4. Lung function tests:
   - Spirometry with reversibility test: Forced expiratory volium income second (FEV1) and Forced vital capacity (FVC) are reduced. Ratio of FEV1/FVC is also reduced. FEV1 or FVC shows >15% and 200 mL improvement after inhalation of bronchodilator (reversibility test). According to Global Initiative for Asthma (GINA), a >12% increase in FEV1 after bronchodilator indicates asthma.
   - PEFR: Reduced. It improves >15% after reversibility test. It may show diurnal variation (seen on waking and before bronchodilator, at afternoon and before going to bed. It shows wide diurnal variation, characteristic of bronchial asthma. Fall of PEF > 20% in early morning is known as morning dipping. It is characteristic of uncontrolled bronchial asthma).
   - Exercise test (fall of FEV1 or PEFR > 15% after 6 minutes exercise indicates exercise induced asthma).
   - Carbon monoxide transfer test (normal in asthma).
5. Blood gas analysis: PaO_2 (reduced)and $PaCO_2$ (raised or normal).
6. Bronchoprovocation test (with methacholine or histamine or hypertonic saline – fall of FEV1 > 20% indicates hyperresponsiveness of airways. This is found in cough variant asthma, mild intermittent asthma, chronic bronchitis with hyperresponsive airways). It is useful when asthma is suspected, but spirometry is not diagnostic.
7. Skin prick test.
8. Allergen provocation tests.
9. Serum IgE level.
10. ECG (to exclude RVH in cor pulmonale).

RELATED QUESTIONS AND ANSWERS

Q. What is **bronchial asthma**?

A. It is a chronic airway inflammatory disorder characterized by hyper-responsiveness of the airways to various stimuli, presenting as breathlessness, cough, chest tightness and wheeze. It is reversible.

Q. What are the **cardinal pathophysiologic features** of bronchial asthma?

A. Three cardinal features:

- Airflow limitation – it is usually reversible spontaneously or with treatment
- Airway hyper-responsiveness – airway is hyper-responsive to a wide range of nonspecific stimuli like exercise, cold air
- Airway inflammation – there is inflammation of the bronchi with infiltration of eosinophils, T cells and mast cells. Also there is plasma exudation, edema, smooth muscle hypertrophy, matrix deposition, mucus plugging and epithelial damage

(In chronic asthma, inflammation may lead to irreversible airflow limitation due to airway wall remodeling, involving the large and small airways with mucus impaction.)

Q. How can you **diagnose** a case of bronchial asthma?

A. Typical history (cardinal features like paroxysmal breathlessness, cough, wheeze and chest tightness) **plus** any of the following:

- FEV1 ≥ 15 % (and 200 mL) increase following the inhalation of bronchodilator. (Global Initiative for Asthma accepts an increase of 12%).
- FEV1 ≥ 15 % decrease after 6 minutes of exercise.
- PEFR shows > 20% of diurnal variation on ≥ 3 days in a week for 2 weeks.

Q. What are the **types** of bronchial asthma?

A. Four groups based on frequency of symptoms, severity of attack and pulmonary function tests abnormality:

1. **Intermittent asthma**: About 2 or less than 2 nocturnal symptoms (cough, wheeze, shortness of breath at night or early morning) in a month. Between the episodes, the patient remains symptom free and lung function tests are normal.
2. **Persistent asthma**: Frequent attacks at least more than two occasions in a month. In between the attack, the patient may or may not have symptoms and lung function tests are abnormal, except in mild case. It may be:
   - Mild – usually the patient has nocturnal attack of dyspnea more than 2 times per month and baseline (i.e. during symptom free state) PEFR or FEV1 is usually < 80 to 65% of predicted value. Occasionally, lung function tests may be normal in between attacks.
   - Moderate – usually the patient has almost daily attack of dyspnea and baseline PEFR or FEV1 is < 65 to 50% of predicted value.
   - Severe – usually the patient has dyspnea to some extent continuously for 6 months or more and baseline PEFR or FEV1 is less than 50% of predicted value.
3. **Acute exacerbation**: Loss of control of any class or variant of asthma. It is again classified as –
   - Mild – The patient is dyspneic, but can complete a sentence in one breath.
   - Moderate – The patient is more dyspneic and cannot complete a sentence in one breath.
   - Severe (severe acute asthma) – The patient is severely dyspneic, talks in words and may be restless, even unconscious.
4. **Special variants**. There are **5** types:
   - Cough variant asthma
   - Exercise induced asthma
   - Occupational asthma
   - Drug-induced asthma (aspirin, other NSAID, β blocker)
   - Seasonal asthma.

Q. What is **cough variant** asthma?

A. It is a type of asthma in which there is chronic dry cough with or without sputum eosinophilia, but no abnormalities in airway function. It is also called eosinophilic bronchitis, common in

young children. Cough is the only symptom, mostly at night. Examination during day may not reveal any abnormality. Cough may be increased with exercise, exposure to dust, strong fragrances or cold air. Methacholine challenge test is positive.

Clinical criteria for diagnosis:

- Dry cough persisting more than 6 to 8 weeks
- Presence of bronchial hyper-responsiveness
- Absence of dyspnea and wheeze.

Treatment: Should be according to the stepwise approach for long-term. Nedocromil sodium is effective. Also consider the following points:

- Allergic rhinitis should be treated, if present.
- Gastroesophageal reflux disease should be treated with proton pump inhibitor (e.g. omeprazole) and/or gastric prokinetic agent (e.g. domperidone).
- Any environmental factors like cold, dust, fume, etc. should be avoided.
- β blocker, aspirin should also be avoided.

Q. What is **exercise-induced asthma**?

A. When exercise produces asthma, it is known as exercise-induced asthma. 10% or more reduction of FEV1 after exercise is diagnostic.

Cold dry air that enters into the lungs during exercise is the main trigger factor. Increased ventilation results in water loss from the pericellular lining fluid of the respiratory mucosa trigger mediator release. Heat loss from the respiratory mucosa is also involved.

Treatment:

- Single dose short acting β_2 agonist, sodium chromoglycate or nedocromil sodium immediately before exercise should be used.
- Inhaled corticosteroid twice daily for 8 to 12 weeks reduces severity.
- If abnormal spirometry and persistent symptoms- inhaled corticosteroid with long acting β_2 agonist.
- Leukotriene receptor antagonist may be used.

Q. What is **occupational asthma**?

A. It may be defined as "asthma induced at work by exposure to occupation related agents, which are mainly inhaled at the workplace". The most characteristic feature is symptoms that worsen on work days and improves on holidays.

Atopic individual and smoker are at increased risk. Commonly found in chemical workers, farmers, grain handlers, cigarette manufacturers, fabric, dye, press and printing workers, laboratory workers, poultry breeders, wood and bakery workers.

Measurement of 2 hourly peak at and away from work is helpful for diagnosis.

Treatment:

- Avoidance of further exposure
- Using mask at work
- If no response, step care asthma management plan.

Q. What is **drug induced asthma**?

A. Symptoms of asthma that occurs after use of certain drugs such as aspirin, beta blocker, some nonsteroidal anti-inframmatory drugs (NSAIDs), etc. These drugs can cause bronchospasm.
Treatment: Avoidance of triggering drugs**.** Safe NSAIDs are paracetamol, tramadol, also etoricoxib.

Q. What is **intrinsic asthma** and **extrinsic asthma**?

A. As follows:

- Intrinsic asthma (non atopic or late onset asthma): When no causative agent can be identified. It is not allergic, usually begins after the age of 30 years, tends to be more continuous and more severe.
- Extrinsic asthma (atopic or early onset asthma): When a definite external cause is present. There is history of allergy to dust, mite, animal danders, pollens, fungi, etc. It occurs commonly in childhood and usually shows seasonal variations.

Q. What are the **differences** between extrinsic and intrinsic bronchial asthma?

A. As follows:

Points	Extrinsic	Intrinsic
1. Age	Early or childhood	Middle age or late onset
2. History of allergy	Usually present	Absent
3. Precipitating allergen	Present	Absent
4. Atopy	Atopic individual	Non atopic
5. Family history of asthma, rhinitis, eczema, etc.	Usually present	Usually absent
6. Skin prick test	Usually positive	Usually negative
7. Serum IgE	High	Normal

Q. What is **acute severe asthma**?

A. It is defined as "severe acute persistent attack of asthma without any remission in between and not controlled by conventional bronchodilator". Previously it was called status asthmaticus.

Q. How to **assess the severity** of acute bronchial asthma?

A. Acute severe asthma is assessed by the following points:

- Inability to complete a sentence in one breath
- Respiratory rate > 25/min
- Pulse rate > 110/min
- PEFR 33 to 50% of predicted (< 200 L/min).

Note

Pulsus paradoxus may be found in up to 45% of acute severe asthma.

Q. What are the features of **life threatening or very severe asthma**?

A. As follows:

- Exhaustion, confusion or coma
- Cyanosis
- Silent chest
- Feeble respiratory effort
- Bradycardia or hypotension or arrhythmia
- PEFR < 33% of predicted (< 100 L/min)
- Blood gas analysis – SpO_2 < 92% or PaO_2 <8 κPa (60 mm Hg) even with O_2
- Normal or raised $PaCO_2$ (> 6 κPa) and low or falling blood pH.

Note

If a patient has raised $PaCO_2$ and/or requires mechanical ventilation with raised inflation pressure, it is called **near fatal asthma.**

Q. How to **treat acute severe bronchial asthma**?

A. As follows:

- High flow O_2—40 to 60% (to maintain O_2 saturation above 92%).
- Nebulized sulbutamol 5 mg or terbutaline 10 mg. May be repeated 2 to 4 hourly.
- Nebulized ipratropium bromide 0.5 mg may be added with nebulized sulbutamol.
- Injection hydrocortison 200 mg IV 4 hourly. After 24 hour, oral prednisolone 60 mg daily should be given for two weeks, then taper**.**
- If no response, IV infusion sulbutamol 3 to 20 µg/min or terbutaline 1.5 to 5 µg/min or magnesium sulphate IV 1.2 to 2 gm over 20 minutes may be given.
- In some cases, injection aminophyllin 5 mg/kg loading dose over 20 minutes, then continuous infusion at 1 mg/kg/h.
- Correction of fluid and electrolytes (repeated use of salbutamol may cause hypokalemia).
- If no response with this regime, the patient may be shifted ICU for assisted ventilation.

Note Remember the following points:

- Arterial blood gases are measured. If $PaCO_2$ > 7 κPa, ventilation should be considered. Chest X-ray should be done in acute severe asthma to exclude pneumothorax
- 2.5 mL of isotonic magnesium sulphate may be given as a nebulizer.

Q. How to monitor a patient with acute severe bronchial asthma?

A. As follows:

- Repeated PEFR in every 15 to 30 min
- Pulse oxymetry (SaO_2 should be kept > 92%)
- Repeat arterial blood gas analysis
- X-ray chest to exclude pneumothorax.

Q. What are the **indications of assisted ventilation?**

A. As follows:

1. Coma, severe exhaustion, confusion, drowsiness, respiratory arrest.
2. Deterioration of arterial blood gas despite optimal therapy:
   - PaO_2 < 8 κPa (< 60 mm Hg) and falling
   - $PaCO_2$ > 6 κPa (> 45 mm Hg) and rising
   - P^H low and falling (H^+ high and rising)
   - Failure to maintain above 92% (or O_2 saturation <90%).

Note. Remember the following points:

- Sedative is contraindicated in acute severe asthma
- No role of chest physiotherapy, antihistamine, antitussive drugs in acute attack.

Q. What is the **stepwise management** of asthma?

A. As follows:

Step	PEFR	Treatment
Step 1. Occasional symptoms (less than once in a week for three months and fewer than two nocturnal symptoms/ month)	100% predicted	Inhaled short acting β_2 agonist as required.If used more than once daily, move to step 2
Step 2. Daily symptoms. Also indicated- – exacerbation of asthma in the last 2 years – uses inhaled â2 agonist 3 times a week or more – symptoms 3 times a week or more – awakened by asthma one night per week	≤ 80% predicted	Add any of the following –· » Low dose inhaled corticosteroid (ICS) – started at 400 µg beclometasone (BDP) or equivalent (budesonide, fluticasone, ciclesonide) daily and may be raised up to 800 µg daily » Leukotriene receptor antagonist (LTRA), theophylline or sodium cromoglicate (these are less effective) » If not controlled, move to step 3
Step 3. Severe symptoms or poorly controlled despite regular use of ICS	50 to 80% predicted	Add one of the following (add on therapy) –· » Low dose ICS + long acting β_2 agonist like salmeterol, formeterol, etc. » Low dose ICS + LTRA » Low dose ICS + sustained release theophylline » Medium or high dose ICS If not controlled, move to step 4
Step 4. Severe symptoms or poorly controlled with high dose inhaled corticosteroids	50 to 80% predicted	High dose inhaled corticosteroid, up to 2000 µg daily Plus regular long acting β_2 agonist Plus either LTRA or modified release theophylline or β_2 agonist.
Step 5. Severe symptoms deteriorating	≤ 50% predicted	Regular oral corticosteroid – add prednisolone 40 mg daily to step 4 and or Anti-IgE treatment
Step 6. Severe symptoms deteriorating inspite of prednisolone	≤ 30% predicted	Hospital admission

Q. What are the **criteria for discharge?**

A. As follows:

- Stable on discharge medication
- Without nebulisation for at least 24 hours
- PEFR 75% of predicted or personal best.

Q. How to **step down**?

A. If patient's asthma is under control, then at every 3 months interval, reduce the dose of inhaled corticosteroids by 25 to 50%.

Q. What are the **steroid sparing** drugs?

A. As follows:

- Methotrexate
- Cyclosporine
- Intravenous immunoglobulin
- Etanercept
- Anti-IgE monoclonal antibody (omalizumab).

Q. What **new therapy** is available for bronchial asthma?

A. As follows:

- Omalizumab, a monoclonal antibody directed against IgE, can be given subcutaneously 2 to 4 weekly
- Bronchoplasty – a stent is applied to dilate constricted bronchi
- Bronchothermoplasty – hyperplastic bronchial smooth muscle is reduced by thermal coagulation.

Q. What is **rescue therapy?**

A. If the patient develops severe asthma or loss of control at any step during therapy, a short course of oral corticosteroid is given. This is called rescue therapy. Tablet prednisolone 30 to 60 mg daily (1 to 2 mg/kg daily for children) is given in a single morning dose or two divided doses for 3 to 14 days. Tapering is not necessary, if it is not given for more than 3 weeks. **Indication**s are:

- Morning symptoms persist till mid-day
- Onset or worsening of sleep disturbance by asthma
- Progressively diminishing response to inhaled bronchodilators
- Symptoms severe enough to require treatment with nebulized or injected bronchodilators
- Symptoms and PEF get progressively worse day by day
- PEFR falls below 60% of patient's personal best recording.

Q. What are the **home management** of acute severe asthma?

A. The patient should follow the rule of 5:

1. The patient should be sitting comfortably in up right position.
2. Give 5 puffs of bronchodilator inhaler with a large volume spacer. Initially 5 puffs (1 puff and 5 sucks) at 5 minutes interval through spacer up to 5 times (25 puffs) within 1 hour. If no improvement, the patient should go to the nearby hospital.
3. If spacer is not available, the patient should take the puffs in the above rule but hold breath for 5 seconds for each puff.

Q. What is **refractory asthma?**

A. Some patients with asthma have more troublesome disease reflected by:

- High medication requirements to maintain disease control or
- Persistent symptoms, asthma exacerbation, or airflow obstruction despite high medication use.

This group is called refractory asthma:

Treatment:

- Home nebulization—continuous or as required
- Vaccination—influenza, measles, pneumococcal vaccine
- Anti-IgE (omalizumab), sublingual immunotherapy
- Disease modifying agent—methotrexate, cyclosporine, gold salt
- Patient's education
- Identifying pitfalls of management.

Q. What is **brittle asthma**?

A. This is an unusual variant of asthma characterized by severe, life-threatening attacks that may occur within hours or even minutes without little or no warning symptoms. Patients are at risk of sudden death although their asthma may be well controlled in between attacks.

Management:

- The patient should be advised to keep emergency supplies of medications at home, in the car and at work.
- There should be oxygen and resuscitation equipments at home and at work.
- Nebulized β_2 agonists should be available at home and at work. Inhaled long acting β_2 agonists with a corticosteroid can be very effective.
- Self injectable epinephrine should be kept at home, at work and should be carried by the patent at all times.
- Prednisolone 60 mg.
- Medic Alert bracelet.

On developing wheeze, patient should attend the nearest hospital immediately. Direct admission to ICU may be required.

Q. What are the **differences** between bronchial asthma and COPD?

A. Key distinguishing feature is the reversibility test. Bronchial asthma is fully reversible with use of bronchodilator which leads to >15% and 200 mL increase in FEV_1 (except in severe persistent asthma). COPD is not fully reversible and the increase in FEV_1 after bronchodilator is < 15%.

The **differences** between bronchial asthma and COPD are:

Parameter	COPD	Bronchial asthma
1. Age of onset	Middle age, usually >40 years	Any age
2. Smoking history	Common, >20 pack years	May or not be present
3. Allergy	Uncommon	Common—rhinitis, eczema, skin prick positive, eosinophilia
4. Family history	Not common	Common
5. Cardinal features	Cough, expectoration and dyspnea	Dyspnea, cough, wheeze, and chest tightness
6. Sputum	Often copious	Infrequent
7. Symptom free period	It is chronic and progressive without any symptom free period	There is recurrent attack but the patient is usually symptom free in between attacks. However, in chronic bronchial asthma, the features may be persistent
8. Dyspnea	Progressive, persistent (with exacerbation)	Intermittent and variable, vary from day to day and peak at night and in early morning
9. Spirometry	Airway obstruction is irreversible	Airway obstruction is reversible
10. Durnal variation of PEFR	Less	More
11. Sputum microscopy	Increased neutrophil and helper T lymphocyte (CD4)	Increased eosinophil and cytotoxic T lymphocyte (CD8)

Contd...

Contd...

12. Bronchodilator response	May not be satisfactory	Usually satisfactory
13. Airway hyper-responsiveness	Absent in 50% cases	Present
14. Destruction of lung parenchyma	Common	Uncommon

Q. What are the **differences** between bronchial asthma and cardiac asthma?

A. As follows:

Features	Cardiac Asthma	Bronchial Asthma
1. History	» Hypertension, IHD, vulvular disease » Family history of hypertension	» History of previous attack of asthma, allergy or rhinitis » Family history of asthma or allergy
2. Age	Usually elderly	Young, but may be any age
3. Symptoms	» Dyspnea » Cough with frothy sputum, often mixed with blood » Wheeze – rare » Sweating – common	» Dyspnea » Cough with little mucoid sputum » Wheeze – common » Sweating – less
4. Signs	» Pulse—pulsus alternans » BP—high (if hypertensive) » Heart— – Cardiomegaly (apex is shifted) – Gallop rhythm may be present – Primary cause (mitral or aortic valvular disease) may be present » Lungs— – Bilateral basal crepitations. In severe case, extensive crepitations – No or little rhonchi	» Pulse—may be pulsus paradoxus » BP—Normal, low in severe case » Heart— – Absent – No – No » Lungs— – Plenty of rhonchi all over the lungs – No or little crepitations
5. CXR	» Pulmonary edema – perihilar opacities (Bat's wing appearance) » Cardiomegaly	» Relatively clear, evidence of infection may be present
6. ECG	Left ventricular hypertrophy, MI, arrhythmia	Normal, only tachycardia may be present

Q. What are the **differences** between wheeze and stridor?

A. As follows:

❖ **Stridor** is a high pitched, loud sound produced by partial obstruction of major airways like larynx, trachea or large bronchi. It is heard both in inspiration and expiration. Causes are—foreign body in larynx or trachea, laryngeal edema (angioedema), laryngeal tumor, vocal cord palsy due to recurrent laryngeal nerve paralysis, tumor, infection (e.g. epiglottitis, acute laryngitis, diphtheria, whooping cough) or inflammation, paratracheal and subcarinal lymphadenopathy pressing over the main bronchi, laryngismus stridulus in tetany. This indicates an emergency condition.

- **Wheezes** are a musical sound heard from a distance, due to small airways obstruction. High pitched wheezes are produced by obstruction in smaller bronchi and low pitched wheezes are produced in larger bronchi. It is present both during inspiration and expiration but prominent during expiration. Wheezes are caused by severe bronchial asthma, chronic bronchitis or COPD or airways obstruction by a foreign body or tumor.

READ THE FOLLOWING TOPICS

Asthma with Diabetes Mellitus

Drugs are used as in other cases of bronchial asthma. However, the following points should be remembered:

- Corticosteroid can be used if necessary, but regular sugar monitoring should be done.
- In severe acute asthma, insulin therapy may be necessary.
- Metformin should be avoided in uncontrolled asthma and contraindicated in acute severe asthma.
- Dose of oral hypoglycemic drugs like sulfonylurea and pioglitazone should be adjusted if used with aminophylline, as it may cause hypoglycemia.

Asthma in Pregnancy

1. Unpredictable clinical course:
   - One third worsen
   - One third improve
   - One third remain stable.
2. Uncontrolled asthma is associated with:
   - Maternal complications – hyperemesis gravidarum, hypertension, pre-eclampsia, vaginal hemorrhage, complicated labor.
   - Fetal complications – IUGR, low birth weight, preterm baby, increased perinatal mortality, neonatal hypoxia.
3. Management of asthma in pregnancy:
   - All inhalers are safe and effective.
   - β_2 agonist (both short and long acting), inhaled steroids, theophylline, oral prednisolone, chromone are safe.
   - If the patient was getting leukotriene receptor blockers, it can be continued.
4. Management during labor: Treatment as usual should be continued. If the patient is on maintenance prednisolone > 7.5 mg/day for > 2 weeks prior to delivery, it should be changed to parenteral hydrocortisone, 100 mg 6 to 8 hourly during labor.
5. Breastfeeding should be continued. Very little drug is excreted in breast milk (<1% of maternal theophylline is excreted in milk).

Note

Acute attack during delivery is rare, probably due to endogenous steroid production. If prostaglandin $F_{2\alpha}$ is needed, it should be used with extreme caution as it may induce bronchospasm.

Asthma with Hypertension

Management of asthma is same. Regarding antihypertensive drugs, remember the following points:

- Avoid β blocker. However, cardioselective β blocker can be used.
- Drug of choice—calcium channel blocker or ARB (losartan, valsartan). ACE inhibitor is avoided as it may induce cough.

Asthma with Arrhythmia

- Digoxin and amiodarone may be used
- Aminophylline or theophylline should be avoided.

Asthma with Pain

- Paracetamol and tramadol are preferred for pain management. COX 2 inhibitor can be used.
- NSAIDs like aspirin, diclofenac, etc. should be avoided
- Steroid may be given, if needed
- DMARDs are safe.

Asthma with Heart Failure

- Diuretic is the drug of choice
- ACE inhibitors should be continued, if tolerated
- Digoxin may be given
- Carvedilol may be used in low doses.

Asthma with IHD

- Antianginal nitrates, calcium channel blocker (diltiazem and verapamil) are drug of choice
- Clopidogrel is preferred than aspirin (as it may trigger or aggravate asthma)
- Sometimes, cardioselective β blocker (like metoprolol) may be given
- Asthma should be well controlled.

CHRONIC BRONCHITIS

CHIEF COMPLAINTS

- Cough with sputum for … years
- Tightness in the chest for … months
- Breathlessness on exertion for … months.

HISTORY

History of present illness: The patient was alright … years back. Since then, he has been suffering from frequent attack of cough with profuse expectoration of mucoid sputum. Initially, cough was present during winter only and persisted for 2 to 3 months. For the last … month, it is present throughout day and night, more marked in the morning and also on exposure to cold and dust. The patient also complains of occasional tightness all over the chest, which is worse on coughing. He also complains of difficulty in breathing, more marked during moderate to severe exertion, relieved by taking rest. There is no history of chest pain, hemoptysis, and paroxysmal nocturnal dyspnea. He does not give any history of fever, swelling of the ankle or weight loss. His bowel and bladder habits are normal.

History of past illness: 2 years back, he was admitted in the hospital due to severe attack of cough and breathlessness.

Family history: Nothing contributory.

Personal history: He is a truck driver, smokes 30 sticks per day for last 35 years.

Drug history: He used to take tablet aminophylline, cough syrup, salbutamol inhaler, beclomethacin inhaler and sometimes local doctor prescribed antibiotics, the name of which he cannot mention.

GENERAL EXAMINATION

- The patient is emaciated
- Central cyanosis present
- No anamia, jaundice, edema, clubbing, koilonychia or leukonychia
- No lymphadenopathy or thyromegaly
- Pulse: 120/min, high volume
- BP: 120/70 mm Hg
- Respiratory rate: 20/min
- JVP: not raised
- (Look at the sputum pot, if available at the bedside).

SYSTEMIC EXAMINATION

Respiratory System

Inspection:

- Shape of the chest: Normal
- Movement of the chest: Bilaterally restricted
- Intercostal space: Appears full.

Palpation:
- Trachea: Central
- Apex beat: in the left 5th intercostal space in the midclavicular line, normal in character
- Chest expansion: Reduced
- Vocal fremitus: Normal.

Percussion:
- Percussion note: Normal resonance
- Area of liver dullness: In the right 5th ICS in midclavicular line
- Area of cardiac dullness: Impaired

Auscultation:
- Breath sounds: Vesicular with prolonged expiration
- Added sounds: Plenty of rhonchi, in both lung fields, present in both inspiration and expiration
- Vocal resonance: Normal

FET (forced expiratory time): 8 seconds (normally <6 seconds).

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr. …, 52 years old, truck driver, normotensive, nondiabetic, smoker, hailing from …, presented with frequent attack of cough with profuse expectoration of mucoid sputum for … years. Initially, cough was present during winter only and persisted for 2 to 3 months. For the last … month, it is present throughout day and night, more marked in the morning and also on exposure to cold and dust. The patient also complains of occasional tightness all over the chest, which is worse on coughing. He also complains of difficulty in breathing, more marked during moderate to severe exertion, relieved by taking rest. There is no history of chest pain, hemoptysis, paroxysmal nocturnal dyspnea. He does not give any history of fever, swelling of the ankle or weight loss. His bowel and bladder habits are normal. 2 years back he was admitted in the hospital due to severe attack of cough and breathlessness. He smokes 30 sticks a day for last 35 years. All the family members are in good health. No such illness in family. He used to take tablet aminophylline, cough syrup, salbutamol inhaler, beclomethasone inhaler and sometimes local doctor prescribed antibiotics, the name of which he cannot mention.

On examination – general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is chronic bronchitis.

Q. What are your **differential** diagnoses?

A. As follows:
- COPD
- Chronic persistent bronchial asthma
- Emphysema
- Bilateral extensive bronchiectasis.

Q. Why not this is COPD?

A. Because in the history, there is frequent attack of cough with profuse expectoration 2 to 3 months in a year during winter. But in COPD, usually there should be breathlessness which is progressive and not fully reversible.

Q. What **investigations** should be done in chronic bronchitis?

A. As follows:

1. Full blood count
2. Chest X-ray PA views (no significant abnormality)
3. ECG (usually normal. In cor pulmonale, there may be features of RVH)
4. Lung function tests:
   - FEV_1 (reduced)
   - FVC (reduced)
   - Ratio of FEV_1: FVC is also reduced (indicates obstructive airway disease).
   - Other tests – residual volume (RV is increased), total lung capacity (TLC is increased), gas transfer (either normal or mildly reduced).
5. PEFR (reduced).
6. Blood gas analysis:
   - PO_2 (reduced)
   - PCO_2 (normal or increased)
   - PH (acidosis).
7. CT scan in some cases.

RELATED QUESTIONS AND ANSWERS

Q. What is **chronic bronchitis?**

A. It is defined as "presence of cough with sputum, not attributable to other causes, on most of the days of at least 3 consecutive months for 2 successive years".

Q. What are the **causes** of chronic bronchitis?

A. Multiple factors are responsible:

- Smoking.
- Exposure to dust, fume, foggy environment (may be occupational). Dampness, sudden change in temperature—all exaggerate chronic bronchitis.
- Infection (*H. influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* – all of these exaggerate chronic bronchitis).

Q. What are the **presentations** of chronic bronchitis?

A. Usual presentations are:

- Cough with sputum expectoration, more marked in the morning, on exposure to cold and during winter. The sputum is mucoid or mucopurulent, usually not associated with hemoptysis.
- Tightness of the chest, and breathlessness on exertion.
- In advanced stage, features of pulmonary hypertension and cor pulmonale are present. The patient looks cyanosed and edematous (blue bloater).

Q. What are the **complications** of chronic bronchitis?

A. As follows:

- Respiratory failure, both type I and type II
- Emphysema
- Secondary polycythemia
- Secondary infection
- Pulmonary hypertension
- Cor pulmonale.

Q. How to **treat** chronic bronchitis?

A. As follows:

1. Smoking must be stopped
2. Avoid air pollution (dust, fume)
3. Control of infection with appropriate antibiotic
4. Bronchodilator:
   - Inhaled β agonist—salbutamol (200 µg 4 to 6 hourly), terbutaline
   - Inhaled antimuscarinic—ipratropium (40 µg 4 hourly), tiotropium (18 µg daily), oxitropium (200 µg BD)
   - Long acting β agonist - salmeterol, formeterol
   - Oral theophylline (in some cases).
5. Inhaled corticosteroid beclomethasone (400 µg BD) or budensonide or fluticasone. In severe case, oral prednisolone 30 mg for 2 weeks, followed by maintenance dose.
6. Mucolytic agents like bromhexine or N-acetylcysteine (200 mg 8 hourly orally for 8 weeks) may be given.
7. Other measures:
   - Chest physiotherapy
   - Exercise and weight reduction, if obese
   - Long-term domiciliary oxygen
   - Pulmonary rehabilitation
   - Annual influenza vaccine, 5 yearly pneumococcal vaccine and *Haemophilus influenzae* vaccine may be given.

Q. What are the indications of **long-term domiciliary oxygen therapy** in COPD?

A. As follows:

1. PaO_2 < 7.3 κPa (55 mm Hg) irrespective of $PaCO_2$ and FEV_1 < 1.5 L.
2. PaO_2 7.3 to 8 κPa (55 to 60 mm Hg) associated with:
   - Pulmonary hypertension
   - Peripheral edema
   - Nocturnal hypoxemia
   - Secondary polycythemia.
3. Carboxyhemoglobin < 3% (in patient who have stopped smoking).
4. Terminally ill patient of whatever cause with PaO_2 < 7.3 κPa.

Note

Arterial blood gases should be measured in clinically stable patients on optimal medical therapy on at least two occasions, 3 weeks apart.

Q. How to **treat** acute exacerbations?

A. As follows:

- Nebulized bronchodilators like terbutaline, ipratropium bromide.
- IV antibiotic to control infection.
- Oxygen inhalation (24%, 1 to 3 L/min).
- IV hydrocortisone and oral steroid (steroid is only used in acute exacerbations and unlike in asthma, it does not influence the course of chronic bronchitis).

Q. How to **differentiate** between emphysema and chronic bronchitis?

A. As follows:

Topic	Emphysema	Chronic bronchitis
1. Definition	It is the permanent distension of alveoli with destruction of their walls distal to the terminal bronchioles	It is defined as the presence of cough with sputum, not attributable to other causes, on most of the days of at least 3 consecutive months for 2 successive years
2. Age	50 to 75 years	Middle age (45 to 50)
3. Appearance	Pink puffer	Blue bloater
4. Body built	Lean and thin	Normal
5. Dyspnea	Severe	Less or no
6. Pursed lip	Present	Absent
7. Cough	Not a feature	Main feature
8. Sputum	No sputum	Mucoid expectoration
9. Cyanosis	Absent	Prominent
10. Hyperinflation	Common	Uncommon
11. Shape of the chest	Barrel shaped	Normal
12. Examination of the lung	On percussion, hyperresonant lungs with obliteration of liver and cardiac dullness and on auscultation, no rhonchi or wheeze	Percussion is normal. On auscultation, plenty of rhonchi
13. Pulmonary hypertension with cor pulmonale	Late feature	Early feature
14. Respiratory failure	Late	Common
15. Secondary polycythemia	Absent or late	Common
16. Arterial blood gas analysis	Normal or low PaO_2, normal $PaCO_2$	Low PaO_2, high $PaCO_2$
17. Diffusing capacity	Reduced	Normal
18. X-ray chest	Hyperinflated lung field, low flat diaphragm, horizontal ribs, tubular heart, bulla	Normal

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

CHIEF COMPLAINTS

- Cough with sputum for … years
- Breathlessness on exertion for … months.

HISTORY

History of present illness: The patient was alright … years back. Since then, he has been suffering from frequent attack of cough with profuse expectoration of mucoid sputum. Cough is present throughout the day and night, more marked in the morning and also on exposure to cold and dust. It is progressively increasing day by day. He also complains of difficulty in breathing, more marked during moderate to severe exertion, relieved by taking rest. His breathlessness is progressively increasing. There is no history of chest pain, hemoptysis, paroxysmal nocturnal dyspnea. He does not give any history of fever, swelling of the ankle or weight loss. His bowel and bladder habits are normal.

History of past illness: The patient was admitted in the hospital 4 times with severe breathlessness in the last 3 years.

Family history: Nothing contributory.

Personal history: He is a shopkeeper, smokes 20 sticks a day for last 30 years.

Drug history: He used to take tablet aminophylline, salbutamol, ketotifen frequently. Sometimes, he used to take different types of inhalers.

GENERAL EXAMINATION

- The patient is ill looking, dyspneic. There is suprasternal and supraclavicular excavation.
- No anemia, cyanosis, jaundice, edema, clubbing, koilonychia or leukonychia.
- No lymphadenopathy or thyromegaly.
- Pulse: 100/min, high volume.
- BP: 110/60 mm Hg.
- Respiratory rate: 30/min.
- JVP: Not raised.
- (Look at the sputum pot, if available at the bedside).

SYSTEMIC EXAMINATION

Respiratory System

Inspection:

- Shape of the chest: Barrel shaped.
- Movement of the chest: Bilaterally restricted.
- Intercostal space: Full.

Palpation:

- Trachea: Central
- Apex beat: Difficult to localize
- Chest expansion: Reduced
- Vocal fremitus: Normal.

Percussion:
- Percussion note: Hyperresonant
- Area of liver dullness: In the right 7th ICS in midclavicular line
- Area of cardiac dullness: Impaired.

Auscultation:
- Breath sounds: Vesicular with prolonged expiration
- Added sounds: Plenty of rhonchi, in both lung fields, present in both inspiration and expiration
- Vocal resonance: Normal.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 48 years old, shopkeeper, normotensive, nondiabetic, smoker, hailing from …, presented with frequent attack of cough with profuse expectoration of mucoid sputum for … years. Cough is present throughout the day and night, more marked in the morning and also on exposure to cold and dust. It is progressively increasing day by day. He also complains of difficulty in breathing, more marked during moderate to severe exertion, relieved by taking rest. His breathlessness is progressively increasing. There is no history of chest pain, hemoptysis, paroxysmal nocturnal dyspnea. He does not give any history of fever, swelling of the ankle or weight loss. His bowel and bladder habits are normal. He was admitted in the hospital 4 times with severe breathlessness in the last 3 years. He smokes 30 sticks a day for last 35 years. He used to take tablet aminophylline, salbutamol, ketotifen frequently. Sometimes, he used to take different types of inhalers. There is no history of such illness in the family.

On examination – general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is chronic obstructive pulmonary disease

Q. Why it is **COPD?**

A. The patient is a heavy smoker, taking ... cigarettes a day for ... years, there is chronic cough with breathlessness, which is progressively increasing day by day.

Q. What are the **differential diagnoses** of COPD?

A. As follows:
- Chronic severe or persistent bronchial asthma
- Bronchiectasis
- Chronic bronchitis
- Congestive cardiac failure.

Q. Why not this is a case of chronic bronchitis?

A. Because chronic bronchitis is defined as the presence of cough with sputum, not attributable to other causes, on most of the days of at least 3 consecutive months for 2 successive years.

Q. What is the basic **difference** between bronchial asthma and COPD?

A. Bronchial asthma is reversible, but COPD is not fully reversible and it is progressive.

Q. How to **confirm** your diagnosis?

A. By spirometry and reversibility test.

Q. What are the **findings** in spirometry?

A. As follows:

- FEV_1 < 80% predicted
- FEV_1: FVC < 70% predicted
- Bronchodilator reversibility test shows <15% increase in FEV_1 after giving bronchodilator.

Q. What **investigations** should be done in COPD?

A. As follows:

1. Complete blood count (there may be polycythemia and increased PCV due to persistent hypoxemia).
2. Chest X-ray PA view (there may be features of hyperinflation – increased translucency, low flat diaphragm, tubular heart, widening of intercostal space, emphysematous bullae).
3. ECG (usually normal. In cor pulmonale, there may be features of RVH).
4. Echocardiogram (may show features of cor pulmonale).
5. Lung function tests:
   - FEV_1 and FVC are reduced. Ratio of FEV_1: FVC is also reduced (indicates obstructive airway disease)
   - Post bronchodilator FEV_1 < 80% of the predicted value and FEV_1/FVC is < 70%
   - Other tests: Lung volumes may be normal or increased. Gas transfer coefficient of carbon monoxide is low, when significant emphysema is present
6. PEFR (reduced).
7. Blood gas analysis:
   - Often normal at rest
   - PO_2 (reduced)
   - PCO_2 (normal or increased)
   - P^H (acidosis).
8. High resolution CT—assessment of COPD, characters of emphysema, particularly bullae.
9. Sputum examination (if superadded infection).
10. β_1 antitrypsin deficiency—may be done in young, nonsmoker patient with basal emphysema.

BRIEF DISCUSSIONS ABOUT CHORONIC OBSTRUCTIVE PULMONARY DISEASE

Q. What is **COPD?**

A. COPD is characterized by airflow limitation, which is not fully reversible. It is usually progressive, and associated with an abnormal inflammatory response of the lung to noxious particles or gases.

FEV_1 < 80% predicted and FEV_1: FVC < 70% predicted. Bronchodilator reversibility test shows <15% increase in FEV_1 after giving bronchodilator.

Q. What are the **mechanisms of airflow limitation** in COPD?

A. As follows:

- Increased mucus production and reduced mucocilliary clearance
- Loss of elastic recoil
- Increased muscle tone
- Pulmonary hyperinflation.

Q. What are the **presentations** of COPD?

A. Usually the patient is above 40 years, male and smoker. There is:

- Chronic cough and sputum production, which is progressively increasing
- Progressive breathlessness
- There may be hemoptysis, edema and morning headache (due to hypercapnia).

Q. What are the **systemic features** in COPD?

A. Muscular weakness, peripheral edema due to impaired salt and water excretion, weight loss due to altered fat metabolism, increased osteoporosis, increased circulating inflammatory markers.

Q. What are the **risk factors or causes** of COPD?

A. Multiple factors may be responsible for COPD, such as:

1. Exposure to:
- Smoking (the most common)—active or passive
- Indoor and outdoor air pollution
- Occupation—exposure to dust, fumes, smokes, chemicals, etc. (e.g. coal miners and those who work with cadmium)
- Urban dweller
- Low socioeconomic status
- Low birth weight
- Poor lung growth which may be due to childhood infections or maternal smoking
- Infections—recurrent lung infection, persistent adenovirus in lung tissue, HIV infection is associated with emphysema
- Cannabis smoking (controversial).

2. Host factors:
- Genetic factors—α_1 antitrypsin deficiency
- Airway hyper-reactivity
- More in male and Caucasians
- Biofuel mass.

Q. What **organisms** are associated with acute exacerbation of COPD?

A. Common organisms: *Haemophilus influenzae* and *Streptococcus pneumoniae*. Other less common organisms are *Moraxella catarrhalis*, *Chlamydia pneumoniae* and *Pseudomonas aeruginosa*.

Q. What are the **complications** of COPD?

A. As follows:
- Pulmonary hypertension
- Cor pulmonale
- Respiratory failure
- Secondary infection
- Polycythemia.

Q. What are the **stages or classification** of COPD?

A. According to the GOLD criteria, classification COPD is as follows:

Stage	Spirometry	Symptoms
0. At risk	Normal	Presence of chronic symptoms (cough, sputum production)
I. Mild	$FEV_1/FVC < 70\%$ $FEV_1 \leq 80\%$ predicted	None or mild
II. Moderate	$FEV_1/FVC < 70\%$ $FEV_1 \leq 50\%$, but $< 80\%$ predicted	Mild to moderate symptoms
III. Severe	$FEV_1/FVC < 70\%$ $FEV_1 \leq 30\%$, but $< 50\%$ predicted	Breathlessness on minimal exertion, e.g. dressing
IV. Very severe	$FEV_1/FVC < 70\%$ $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure	Breathlessness at rest

Q. How to **manage** COPD?

A. As follows:

1. Smoking must be stopped
2. Avoidance of dust, fume, smoke, etc
3. Drug therapy according to the stage:

I: Mild	» Avoid of risk factors, influenza vaccination » Short acting inhaled bronchodilator like β_2 agonist (salbutamol, terbutaline) or anticholinergic (ipratropium) when needed
II: Moderate	Above treatment plus: » Regular treatment with one or more long acting bronchodilator like β_2 agonist (e.g. salmeterol, formeterol) or anticholinergic (tiotropium) when needed » Rehabilitation
III: Severe	Above treatment plus: » Inhaled steroid (fluticasone)
IV: Very severe	Above treatment plus: » Long-term oxygen, if chronic respiratory failure » Surgical treatment, if needed

4. Other therapy:
   - Oxygen, if needed
   - Mucolytic (acetylcysteine)
   - Antibiotic (if infection)
   - Diuretic (if edema)
   - Pulmonary rehabilitation
   - Pneumococcal vaccination.
   - Reduction of obesity.
5. Surgical intervention:
   - Bullectomy: If young patient, large bullae compressing surrounding lung tissue, no generalized emphysema
   - Lung volume reduction surgery (LVRS): Predominant upper lobe emphysema, preserved gas transfer, no evidence of pulmonary hypertension
   - Lung transplantation.

Q. How **domiciliary oxygen** is given? What is the **aim** of the therapy?

A. Oxygen O_2 is given 2 to 4 L/min for 15 hours/day by nasal prongs. The aim is to increase the PaO_2 to at least 8 kPa (60 mm Hg) at sea level during rest or SaO_2 to at least 90% (greater benefit may be seen in patients who receive > 20 hours per day).

Note Regarding air travel:

- Preflight assessment should be done by spirometry and hypoxic challenge test with 15% oxygen. If saturation is maintained >90%, the patient can be allowed to travel. If not, air travel should be avoided or undertaken only with inspired oxygen therapy.
- Sufficient supplementary oxygen should be given during flight to keep the PaO_2 above 50 mm Hg, which is achieved by increasing the flow by 1 to 2 L/min.
- Patient who use to take continuous oxygen at home will require this supplementation.

Q. What is the role of **inhaled steroid** in COPD?

A. Inhaled steroid is recommended for symptomatic patient with moderate to severe COPD and for patients with frequent exacerbations, but not in mild COPD. It reduces the frequency and severity of exacerbation. There is small improvement of FEV_1, but it does not alter the natural history of FEV_1 decline.

Q. What is the role of **oral steroid** in COPD? What are the indications of steroid in COPD?

A. Oral steroid is useful during exacerbation, but maintenance therapy should be avoided.

Indications are:

- Stage III or IV disease
- In stage II if oral steroid trial shows responsiveness
- Severe exacerbations of COPD
- Frequent episodes of exacerbations.

Q. What is the **prognosis** of COPD?

A. Prognosis of COPD is predicted by **BODE** index:

Variable	Points on BODE index			
	0	1	2	3
1. **B**ody mass index	> 21	≤ 21		
2. **O**bstruction to airflow (FEV_1 % predicted)	≥ 65	50 to 64	36 to 49	≥ 35
3. **D**yspnea (MMRC scale)	0 to 1	2	3	4
4. **E**xercise capacity (metres walked in 6 minutes)	≥ 350	250 to 349	150 to 249	≤ 149

4 years mortality rate for BODE index 0 to 2 is 10%, while that of BODE index 7 to 10 is 80%.

Note

Poor prognostic factors are increasing age (inversely related), fall of FEV_1 over time, weight loss and pulmonary hypertension.

Q. How to manage **acute exacerbation** of COPD (type II respiratory failure)?

A. As follows:

- Oxygen: Continuous low concentration oxygen via Venturi mask to raise PaO_2 > 8 κPa (60 mm Hg). Initially 24% or 28% oxygen is given and increased gradually provided $PaCO_2$ does not rise unacceptably. If $PaCO_2$ rises and pH falls below 7.25, artificial ventilation or a respiratory stimulant should be given.
- Bronchodilator nebulized short acting β_2 agonist (e.g. salbutamol) with an anticholinergic agent (e.g. ipratropium).
- Oral prednisolone 30 mg daily for 10 days.
- Antibiotic: Given if infection is suspected.
- Diuretic: If peripheral edema.
- Chest physiotherapy. Secretions should be removed by suction.

- Respiratory support: If above treatment fails or there is tachypnea and acidosis (pH < 7.35). Noninvasive ventilatory technique like BiPAP is used first. CPAP is occasionally needed.
- Respiratory stimulant: Less used. Doxapram 1.5 to 4.0 mg/min by slow IV infusion may be helpful.

Note

Many patients with exacerbation of COPD can be managed at home with increased bronchodilator, short course of oral steroid and antibiotic**.**

Indications of hospitalization are:

- Severe symptoms or acute worsening that fail to respond to outpatient management
- Presence of cyanosis
- Peripheral edema
- Alteration of consciousness
- Co-morbidity and poor social circumstances.

Q. Why **low concentration O_2** given in COPD? Or what happens when high flow O_2 given**?**

A. In COPD, the patient is dependent on hypoxic drive for respiration. High flow oxygen blunts the chemoresponsiveness of the respiratory center in the medulla (part of the brainstem) and thus aggravates respiratory failure (Type 2 respiratory failure). To avoid this, low flow oxygen is given.

Q. What are the **discharge criteria** of COPD patient?

A. As follows:

- The patient should be clinically stable and no parenteral therapy for 24 hours
- Inhaled bronchodilators are required less than 4 hourly
- Oxygen delivery has ceased for 24 hours
- The patient is able to eat and sleep without significant episodes of dyspnea
- The patient or caretaker understands and is able to administer medications
- Follow up and home care arrangements (As for example home oxygen, home care, Meals on Wheels, community nurse, allied health, GP, specialist) have been completed
- The patient is ambulating safely and independently, and performing activities of daily living.

CHRONIC BRONCHITIS WITH EMPHYSEMA

CHIEF COMPLAINTS

- Cough with sputum for … years
- Breathlessness on exertion for … months.

HISTORY

History of present illness: The patient was alright … years back. Since then, he has been suffering from frequent cough with profuse expectoration of mucoid sputum. Initially, cough was present during winter only and persisted for 2 to 3 months. For the last … months, it is present during the day and night, more marked in the morning and also on exposure to cold and dust. He also complains of difficulty in breathing, which was more marked during moderate to severe exertion. But for the last ... months, breathlessness is more even during mild exertion, such as undressing, going to the toilet, climbing upstairs, etc. There is no history of chest pain, hemoptysis, and paroxysmal nocturnal dyspnea. He does not give any history of fever, swelling of the ankle or weight loss. His bowel and bladder habits are normal.

History of past illness: He is suffering from chronic bronchitis for the last 10 years but non-hypertensive, nondiabetic.

Family history: There is no such illness in his family.

Personal history: He was a previous smoker, but stopped for the last 2 years. He works in a jute mill.

Drug history: He used to take tablet aminophylline, salbutamol, etc. Also he took some inhalers, the name of which he cannot mention.

GENERAL EXAMINATION

- The patient is emaciated and dyspneic with pursing of lips.
- There is suprasternal and supraclavicular recession with prominent accessory muscles of respiration.
- No anaemia, cyanosis, edema, clubbing, koilonychia, leukonychia.
- Pulse:124/min.
- BP: 120/75 mm Hg.
- Respiratory rate: 30/min.

SYSTEMIC EXAMINATION

Respiratory System

Inspection:

- Chest is barrel-shaped
- Indrawing of the lower intercostal space on inspiration (due to low flat diaphragm, called Harrison's sulcus).

Palpation:

- Trachea is central, tracheal tug (descent of trachea during inspiration) is present.
  - Cricosternal distance (distance between suprasternal notch and cricoid cartilage): Reduced (normally 3 fingers or more)
  - Apex beat is not felt
  - Chest expansion: Reduced (tell in centimeter)
  - Vocal fremitus: Reduced in both sides.

Percussion:
- Hyper-resonance in both the lung fields.
- Obliteration of the liver and cardiac dullness (liver dullness may be lowered down).

Auscultation:
- Breath sound – Diminished and vesicular with prolonged expiration.
- Plenty of rhonchi are present in both lung fields.
- Vocal resonance—reduced.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 49 years old, jute mill worker for 25 years, normotensive, nondiabetic, ex-smoker, hailing from …, presented with frequent cough with profuse expectoration of mucoid sputum for ... years. Initially, cough was present during winter only and persisted for 2 to 3 months. For the last … month, it is present during the day and night, more marked in the morning and also on exposure to cold and dust. He also complains of difficulty in breathing, which was more marked during moderate to severe exertion. But for the ... months, breathlessness is more even during mild exertion such as undressing, going to the toilet, climbing upstairs etc. There is no history of chest pain, haemoptysis, paroxysmal nocturnal dyspnoea. He does not give any history of fever, swelling of the ankle or weight loss. His bowel and bladder habits are normal. He used to take tablet aminophylline, salbutamol etc. Also he took some inhalers, the name of which he cannot mention. He was a previous smoker, but stopped for the last 2 years. There is no history of similar illness in his family.

On examination – general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is chronic bronchitis with emphysema

Q. What are your **differential diagnoses?**

A. As follows:
- COPD
- Bronchial asthma
- Cardiac failure.

Q. Why not COPD?

A. Because, COPD is characterized by airflow limitation, which is not fully reversible. It is usually progressive, and associated with an abnormal inflammatory response of the lung to noxious particles or gases.

Q. Why not CCF?

A. Because, in CCF, there should be engorged and pulsatile neck veins, enlarged tender liver, dependent pitting oedema.

Q. What **investigations** should be done in emphysema?

A. As follows**:**

1. X-ray chest P/A view (shows features of emphysema):
   - Increased translucency of both lung fields with loss of peripheral vascular markings
   - Low flat diaphragm
   - Tubular heart
   - Widening of intercostal space and ribs appear horizontal
   - Bulla may be present (which is pathognomonic)
   - Prominent pulmonary arterial shadow in both hilum (due to pulmonary hypertension).

2. Lung function tests:
   - FEV_1 and FVC are reduced. Ratio of FEV_1: FVC is reduced (obstructive type)
   - Post-bronchodilator FEV_1 is <80% predicted, and ratio of FEV1:FVC is <70% predicted
   - PEFR: reduced
   - Lung volume with increased TLC and RV.
3. Arterial blood gas analysis:
   - Low PCO_2 (due to hyperventilation)
   - Low PO_2
   - Impaired gas transfer of CO.
4. Other investigations:
   - TC, DC, Hb%, ESR (polycythemia may be present).
   - CT scan of the chest, especially HRCT (high resolution CT)—highly suggestive.
   - To confirm—biopsy of the lung tissue (not a routine test).
   - In young patient, serum level of α_1 antitrypsin may be done.
   - ECG may show tall P, RVH, RAD in patient with corpulmonale.
   - Echocardiography.

Q. What is the **definitive diagnosis** of emphysema?

A. Histopathological.

RELATED QUESTIONS AND ANSWERS

Q. What is emphysema?

A. It is the permanent distension of alveoli with destruction of their walls distal to the terminal bronchioles.

Q. What are the **presentations** of emphysema?

A. Breathlessness on exertion and minimum cough with lip pursing.

Q. What are the **types** of emphysema?

A. Four types:

- Centriacinar: Involves the proximal part of acini, limited to respiratory bronchiole with relatively less change in acinus.
- Panacinar: All the alveoli and alveolar ducts in acinus are involved, both central and peripheral portion. It occurs mostly in α_1-antitrypsin deficiency.
- Paraseptal: Along the septa, blood vessels and pleura.
- Scar or irregular emphysema: Scarring and damage affecting the lung parenchyma without involving acinus structure.

Q. What are the **causes** of emphysema?

A. As follows:

- Smoking
- Cold, dust (causes centrilobular emphysema)
- α_1-antitrypsin deficiency
- Macleod's syndrome (unilateral emphysema).

Q. How **smoking** cause emphysema?

A. Certain mechanisms are responsible:

- Prolonged smoking causes inflammation in airways, release of oxidants and proteinase from inflammatory cells, which are responsible for irreparable damage to the supporting connective tissue of alveolar septa
- There is increased proteinase synthesis and inactivation of anti-proteinase due to enzymes responsible for inactivating anti-proteinase
- Imbalance between proteinase and anti-proteinase.

Q. Why **lip pursing** is present in emphysema?

A. By this in expiration through partly closed lips, there is increased end-expiratory pressure that keeps airway open, helping to minimize air trapping.

Q. What are the **complications** of emphysema?

A. As follows:

- Pulmonary hypertension
- Cor pulmonale
- Respiratory failure type 1
- Bullae, which may rupture causing pneumothorax
- Secondary infection
- Polycythemia.

Q. What are the **signs** of emphysema**?**

A. As follows:

- Patient is dyspneic with lip pursing
- Barrel shaped chest
- Suprasternal and supraclavicular excavation during inspiration
- Prominent sternomastoid and scalene muscles
- Tracheal tug
- Reduced cricosternal distance (length of trachea above suprasternal notch)
- Indrawing of lower intercostal space during inspiration
- Horizontal ribs with wide intercostal spaces
- Wide subcostal angle
- Obliteration of liver and cardiac dullness.

Q. How to **treat** emphysema?

A. As follows:

1. Smoking must be stopped.
2. For breathlessness:
   - Inhaled salbutamol (200 mg 4 to 6 hourly) or ipratropium (40 mg 4 hourly) or tiotropium (18 mg daily) or oxitropium (200 mg BD)
   - If no response, inhaled corticosteroid beclomethasone (400 ìgm BD)
   - In severe case, oral prednisolone 30 mg for 2 weeks, followed by maintenance dose.
3. Antibiotic, if secondary infection.
4. In chronic cough: Mucolytic therapy (acetylcysteine 200 mg 8 hourly orally for 8 weeks).
5. Domiciliary O_2 may be given
6. Vaccination, such as annual influenza vaccine, 5 yearly pneumococcal vaccine and *Haemophilus influenzae* vaccine may be given.
7. Other treatment:
   - α_1-antitrypsin in case of deficiency
   - Lung transplantation in young patient
   - Surgical intervention (if large bullae)
   - Weight reduction, if obese
   - Exercise.

Q. What is bullae? What are the **causes**? What is the **treatment**?

A. It is the thinwalled air space produced by rupture of alveolar walls. Bullae may be single or multiple, large or small, and usually associated with emphysema. It is usually situated subpleurally. Rupture may lead to pneumothorax. Large bullae may compress the lung tissue and impair lung function. Causes of bullae are:

- Emphysema
- Congenital (rare).

Treatment:

- Small bullae: No treatment, treatment of primary cause
- Large bullae with impaired lung function requires surgical ablation of bullae.

Q. What is **pink puffer** and **blue bloater**?

A. As follows:

Pink puffer:

- The patient is not cyanosed (pink), but dyspneic with lip pursing (puffer). No edema
- Usually lean and thin
- It is found in emphysema, commonly panacinar, age 50 to 75 years
- Usually there is no cor pulmonale
- Exertional dyspnea is the main feature, and cough less common
- Arterial PO_2 and PCO_2 are relatively normal.

Blue bloater:

- The patient is cyanosed (blue) and edematous (bloater). But not dyspneic (or mild dyspnea)
- It is found in chronic bronchitis, age 40 to 45 years. Edema is due to cor pulmonale
- Cough with sputum is the main feature, dyspnoea is less common
- Pulmonary hypertension, right ventricular hypertrophy, cor pulmonale and secondary polycythemia may develop (patient may appear plethoric)
- There is marked arterial hypoxemia and hypercapnia (low PO_2 and increased PCO_2).

Q. What are the **indications** of long term domiciliary (home) oxygen therapy?

A. As follows:

- Severe hypoxemic patients, PO_2 < 7.3 κPa (55 mm Hg) or SaO_2d < 88%, with or without hypercapnia, FEV1 < 1.5 L
- PO_2 between 7.3 to 8.0 κPa (55 to 60 mm Hg) or SaO_2 at 89% with evidence of cor pulmonale, CCF or polycythemia (Hct >55%).

Note

Oxygen is given 2 to 4 L/min, 15 hours/day. The patient must stop smoking.

Q. What is **Macleod's syndrome?**

A. It is a type of unilateral emphysema due to childhood bronchitis or bronchiolitis, resulting in subsequent impairment of alveolar growth. It is a rare disease (also called **Swyer-James syndrome**).

Q. What are the causes of **dyspnea on exertion?**

A. As follows:

- COPD
- Bronchial asthma
- DPLD (Interstitial lung disease)
- LVF
- Valvular diseases of the heart
- Anemia.

CHRONIC BRONCHITIS WITH COR PULMONALE

CHIEF COMPLAINTS

- Cough with sputum for … months.
- Breathlessness for … months.
- Swelling of both legs for … months.

HISTORY

History of present illness: The patient was alright … months back. Since then, he has been suffering from cough, which is more marked in the morning. There is expectoration of copious amount of sputum, which is mucoid or mucopurulent in nature but not mixed with blood. The patient mentioned that he has been experiencing episodic attack of such illness for almost 10 years, mostly during the winter seasons and each episode persisted for 3 to 4 months. Along with cough, he is also experiencing breathlessness which was initially associated with moderate to severe exertion, but now with even mild exertion. There is no history of paroxysmal nocturnal dyspnea or orthopnea. For … months, he noticed gradual swelling of his feet, more marked with prolonged standing and disappears on waking in the morning. He also complains of upper abdominal discomfort associated with loss of appetite. There is no history of fever, burning micturition, yellow coloration of urine or sclera, abdominal swelling and weight loss. His bowel and bladder habits are normal.

History of past illness: He has been suffering from chronic bronchitis for the last ... year.

Family history: There is no such illness in his family.

Personal history: He smokes 20 sticks per day for last 15 years, but nonalcoholic

Drug history: He took tablet aminophylline, salbutamol, occasional cough syrup and sometimes inhalers.

GENERAL EXAMINATION

- The patient looks anxious, emaciated
- Central cyanosis: Present
- Bilateral pitting pedal edema: Present
- No anemia, jaundice, clubbing, koilonychia or leukonychia
- No lymphadenopathy or thyromegaly
- Pulse: 120/min, bounding pulse
- BP: 120/70 mm Hg
- Respiratory rate: 30/min
- JVP: Raised with prominent “a” wave.

SYSYEMIC EXAMINATION

Respiratory System

Inspection:

- Shape of the chest: Barrel shaped
- Movement of the chest: Bilaterally restricted
- Suprasternal and intercostal recession present.

Palpation:
- Chest expansion: Reduced
- Trachea: Central
- Tracheal tug: Present
- Apex beat: Difficult to localize
- Vocal fremitus: Reduced.

Percussion:
- Percussion note: Hyperresonant in both sides of chest
- Area of liver dullness: In the right 7th ICS in midclavicular line
- Area of cardiac dullness: Impaired.

Auscultation:
- Breath sound: Vesicular with prolonged expiration
- Added sound: Plenty of rhonchi, in both lung fields, both in inspiration and expiration. There are a few coarse crepitations present
- Vocal resonance: Reduced.

SYSTEMIC EXAMINATION

Cardiovascular System

- **JVP:** Engorged and pulsatile JVP, prominent 'a' wave
- **Pulse:** 120/min
- **BP:** 120/70 mm Hg.

Examination of precordium:

Inspection:
- Visible epigastric impulse.

Palpation:
- Apex beat: In left 5th intercostal space ... cm from midline.
- Thrill: Absent
- Palpable P_2, left parasternal lift and epigastric pulsation: Present.

Percussion: area of cardiac dullness is impaired.

Auscultation:
- 1st heart sound: Normal in all the areas
- 2nd heart sound: P_2 is loud in pulmonary area.

Abdomen

Inspection:
- Visible peristalsis.

Palpation:
- Liver is enlarged 4 cm from right costal margin in right midclavicular line, soft, tender, margin is sharp, surface is smooth, no hepatic bruit
- Spleen is not palpable.

Percussion:
- No abnormality.

Auscultation:
- Bowel sound present
- No hepatic bruit.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 52 years old, businessman, normotensive, nondiabetic, smoker, hailing from …, presented with cough for … months, which is more marked in the morning. There is expectoration of copious amount of sputum, which is mucoid or mucopurulent in nature but not mixed with blood. The patient mentioned that he has been experiencing episodic attack of such illness for almost 10 years, mostly during the winter seasons and each episode persisted for 3 to 4 months. Along with cough, he is also experiencing breathlessness which was initially associated with moderate to severe exertion, but now with even mild exertion. There is no history of paroxysmal nocturnal dyspnea or orthopnea. For … months, he noticed gradual swelling of his feet, more marked with prolonged standing and disappears on waking in the morning. He also complains of upper abdominal discomfort associated with loss of appetite. There is no history of fever, burning micturition, yellow coloration of urine or sclera, abdominal swelling and weight loss. His bowel and bladder habits are normal. He smokes 20 sticks a day for last 15 years. He took tablet aminophylline, salbutamol, occasional cough syrup and sometimes inhalers. There is no such illness in his family.

On examination – general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is chronic bronchitis with cor pulmonale.

Q. What are the **differential diagnoses?**

A. As follows

- CCF
- CLD
- Nephrotic syndrome.

Q. Why **cor pulmonale**?

A. Because he has been suffering from chronic bronchitis for the last ... years, and there are features of right sided heart failure. So his failure is secondary to the disease of the lung, which indicates cor pulmonale.

Q. Why not **CLD**?

A. In the history, there is no history of jaundice or other liver disease and on physical examination there are no stigmata of CLD.

Q. Why not **nephrotic syndrome**?

A. Nephrotic syndrome is characterized by generalized edema, massive proteinuria and hypoalbuminemia. In this case, there is no history of generalized edema. In contrast, there is history of chronic bronchitis and also there are features of right sided heart failure, which are not consistent with nephrotic syndrome.

Q. What **investigations** are done in cor pulmonale?

A. As follows:

- X-ray chest PA view: May show right ventricular enlargement and right atrial dilatation. Pulmonary arteries are prominent, peripheral lung fields are oligemic
- ECG: May show RVH and right atrial hypertrophy
- Echocardiogram: Shows right ventricular dilatation and/or hypertrophy
- Lung function tests
- Others: CBC, arterial blood gas analysis, CT scan of chest, pulmonary artery wedge pressure.

RELATED QUESTIONS AND ANSWERS

Q. What is **cor pulmonale**?

A. Cor pulmonale may be defined as "right ventricular hypertrophy or dilatation with or without right sided heart failure due to causes of lung parenchyma, pulmonary vasculature or chest wall".

Q. What are the **types** of cor pulmonale?

A. Acute and chronic.

- Acute: It occurs following massive pulmonary embolism with acute pulmonary hypertension causing right ventricular dilatation and failure (no RVH). May occur in ARDS.
- Chronic: It is defined as "right ventricular hypertrophy or dilatation with or without right sided heart failure due to causes of lung parenchyma, pulmonary vasculature or chest wall".

Q. What are the **causes** of chronic cor pulmonale?

A. As follows:

1. Respiratory disorders:
   - Obstructive: COPD or chronic bronchitis with emphysema, chronic persistent asthma
   - Restrictive: DPLD (interstitial lung disease).
2. Pulmonary vascular disorders:
   - Primary pulmonary hypertension
   - Vasculitis of the small pulmonary arteries.
3. Chest wall or bony abnormality: kyphoscoliosis, ankylosing spondylitis, obesity (Pickwickian syndrome).

Q. What are the **signs of pulmonary hypertension** (PH)?

A. Signs of pulmonary hypertension are:

- Low volume pulse
- JVP is raised
- Prominent 'a' wave in JVP
- Left parasternal heave (indicates RVH)
- Palpable P_2
- Loud P_2 on auscultation
- Epigastric pulsation (indicates RVH)
- Early diastolic murmur (Graham Steel murmur due to pulmonary regurgitation).

Q. What are the **signs** of chronic cor pulmonale?

A. Signs of primary disease like COPD, emphysema, etc. **plus**:

1. Without failure:
   - Signs of pulmonary hypertension and RVH (palpable P2, left parasternal heave, epigastric pulsation).
2. With failure:
   - Engorged and pulsatile neck vein
   - Enlarged tender liver
   - Dependent edema (pitting, pedal edema).

Q. What are the causes of **right heart failure**?

A. As follows:

- Secondary to left sided failure (the most common cause)
- Secondary to mitral stenosis
- Cor pulmonale

- Myocardial infarction
- Pulmonary valvular disease (PS, PR)
- Tricuspid regurgitation
- Eisenmenger's syndrome (pulmonary hypertension with reversal of shunt in ASD, VSD, PDA)
- Cardiomyopathy
- Chronic constrictive pericarditis.

Q. How to **manage** cor pulmonaly?

A. As follows:

1. Treatment of cardiac failure:
   - Diuretic (frusemide)
   - Fluid and salt restriction
   - Vasodilator drug
   - Digoxin is some cases.
2. Treatment of the underlying cause, as for example COPD.
3. Sildenofil in primary pulmonary hypertension.
4. Venesection: If hematocrit is more than 55%.
5. Domiciliary oxygen.

Q. What is the **prognosis** of cor pulmonale?

A. Approximately 50% patients die within 5 years.

Q. What is **Pack-year**?

A. It is a way to measure the amount a person has smoked over a long period of time. It is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked.

For example, 1 pack year is equal to smoking 20 cigarettes (1 pack) per day for 1 year, or 40 cigarettes per day for half a year, and so on.

One pack year equals 365 packs of cigarettes.

BRONCHIECTASIS

CHIEF COMPLAINTS

- Cough with copious sputum for … months
- Occasional hemoptysis for … months
- Weight loss, weakness and malaise for … months.

HISTORY

History of present illness: The patient was alright … months back. Since then, he has been suffering from frequent cough with profuse expectoration of mucoid sputum, which is more marked in the morning after waking from sleep. Occasionally, the sputum is purulent or yellowish and foul smelling, relieved after taking antibiotics. The patient also noticed small amount of blood occasionally mixed with sputum. For the last ... months, he also complains of loss of about 5 kg body weight, weakness, malaise, occasional fever and night sweats. There is no history of chest pain, breathlessness or swelling of the ankle. His bowel and bladder habits are normal.

History of past illness: He was suffering from measles at the age of 6 and also from recurrent chest infection for the last 2 years. There is no history of whooping cough, pulmonary TB or foreign body impaction.

Family history: There is no family history of such illness.

Personal history: He smokes about 30 sticks a day for last 10 years, but nonalcoholic.

Drug history: He used to take cough syrup frequently, treated with antibiotics several times due to chest infection.

GENERAL EXAMINATION

- The Patient is slightly emaciated
- There is generalized clubbing involving both toes and fingers, but no hypertrophic osteoarthropathy
- No anemia, jaundice, cyanosis, edema, koilonychia or leukonychia
- No thyromegaly or lymphadenopathy
- Pulse: 88/min
- BP: 120/75 mm Hg
- Respiratory rate: 30/min
- (Examination of the sputum cup: Always look at the cup at the side of the patient, if any).

SYSTEMIC EXAMINATION

Respiratory System

Inspection:

- Chest movement slightly restricted (mention where). Or, no abnormality.

Palpation:

- Trachea: Central
- Apex beat: In left 5th intercostal space 9 cm from the midsternal line, normal in character
- Vocal fremitus: Slightly increased on both base
- Chest expansion: Normal.

Percussion:
- Percussion note: Normal
- Liver and cardiac dullness: In normal area.

Auscultation:
- Breath sound: Normal vesicular (may be bronchial over the involved area).
- There are multiple coarse crepitations on the base of both lungs, both in inspiration and expiration, reduced (or disappeared) after coughing.
- Vocal resonance: Slightly increased (mention where).

Other systemic examination reveals no abnormalities.

SALIENT FEATURES

Mr. …, 28 years old, day laborer, normotensive, nondiabetic, smoker, hailing from …, presented with frequent cough with profuse expectoration of mucoid sputum for ... months. It is more marked in the morning after waking from sleep. Occasionally, the sputum is purulent or yellowish and foul smelling, relieved after taking antibiotics. The patient also noticed small amount of blood occasionally mixed with sputum. For the last ... months, he also complains of loss of about 5 kg body weight, weakness, malaise, occasional fever and night sweating. There is no history of chest pain, breathlessness or swelling of the ankle. His bowel and bladder habits are normal. There is history of measles during childhood. He also gives history of recurrent chest infection for the last 2 years. There is no history of whooping cough, pulmonary TB or foreign body impaction. There is no family history suggestive of such illness. He smokes about 30 sticks a day for last 10 years but nonalcoholic. He used to take cough syrup frequently, treated with antibiotics several times due to chest infection.

On examination – general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is bilateral bronchiectasis.

> **Note**
>
> All the above signs may be on the left or right side. Then the diagnosis will be left or right sided bronchiectasis.

Q. What are your differential diagnoses?

A. As follows:
- DPLD (IPF)
- Pulmonary TB.

Q. Why it is bronchiectasis?

A. The patient is complaining of cough with profuse expectoration of sputum, more marked in the morning after waking up from sleep. On examination, there are generalized clubbing and bilateral basal coarse crepitations, altered by coughing. All are highly suggestive of bronchiectasis.

Q. Why not IPF?

A. In such case, usually there is history of persistent cough may or may not be with profuse expectoration, progressively increasing breathlessness or exertional dyspnea. There are bibasal fine late inspiratory crepitation (like unfastening of Velcro).

Q. What **investigations** do you suggest in bronchiectasis?

A. As follows:

1. Chest X-ray PA view (may be normal). There may be:
- Ring with clear centre (like honeycomb)
- Ring with or without fluid level, may be multiple (cystic bronchiectasis)
- Linear streaks (tram line)
- Thick bronchi, signet ring or patchy opacity.

2. High-resolution CT scan: Definitive (preferred investigation).

3. Others:
- CBC with ESR (may be neutrophilic leucocytosis)
- X-ray PNS (in Kartagener's syndrome)
- Lung function tests (obstructive type usually, may be restrictive in advanced case)
- Sputum for Gram staining, C/S, AFB, malignant cell (mention if necessary according to the history)
- Sometimes bronchoscopy to locate the site of obstruction
- Aspergillus precipitin antibody or skin prick test (if ABPA is suspected)
- Serum immunoglobulin: If hypogammaglobulinemia is suspected (10% of adults with bronchiectasis have antibody deficiency, mainly IgA)
- Sweat test for sodium and chloride content: If cystic fibrosis is suspected (sweat chloride content > 60 mEq/L is suggestive of cystic fibrosis)
- Mucociliary clearance (nasal clearance of saccharin): Normally less than 30 minutes. If more, it indicates ciliary dysfunction
- Urine for proteinuria (if amyloidosis is suspected)
- USG of whole abdomen (if situs inversus is suspected).

Q. If a patient with bronchiectasis develops **nephrotic syndrome** (or urine shows proteinuria), what is the likely diagnosis?

A. Amyloidosis (in amyloidosis, there may be splenomegaly). In long standing bronchiectasis, amyloidosis may occur as a complication.

Q. What is the **role of CT scan** in the diagnosis of bronchiectasis?

A. Conventional CT scan has sensitivity of 60 to 80% while high resolution CT scan has a sensitivity of more than 90% (previously bronchography was done).

Q. What is the **difference** between standard CT scan and HRCT?

A. In standard CT scan, the resolution is 10 mm thick. But in HRCT, resolution is 1 to 2 mm thick.

RELATED QUESTIONS AND ANSWERS

Q. What is **bronchiectasis** and what are the **causes** of it?

A. It is the abnormal, permanent dilatation of one or more bronchi with destruction of bronchial wall proximal to the terminal bronchiole. Causes are:

1. Congenital or hereditary:
- Cystic fibrosis
- Kartagener's syndrome (triad of bronchiectasis, dextrocardia and sinusitis or frontal sinus agenesis)
- Primary ciliary dyskinesia (including immotile ciliary syndrome)
- Hypogammaglobulinemia (of IgA and IgG. It causes recurrent infection and bronchiectasis)
- Yellow nail syndrome

- Young's syndrome (obstructive azoospermia and chronic sinopulmonary infection, thought to be due to mercury intoxication)
- Sequestrate segment of lung.

2. Acquired:

- In children, pneumonia complicating measles, whooping cough, primary TB and foreign body
- In adults, bronchial neoplasm, pulmonary TB, recurrent aspiration or suppurative pneumonia
- Allergic bronchopulmonary aspergillosis (causes proximal bronchiectasis)

Note

In children, post-measles or whooping cough are commonly associated with bronchiectasis. In adult, post-tubercular bronchiectasis is the common one.

Q. What are the **types** of bronchiectasis?

A. Three types:

- Saccular or cystic (more severe form).
- Cylindrical.
- Fusiform.

Q. What is the **most common site** of bronchiectasis?

A. Left lower lobe and lingula.

Q. What are the **presentations** of bronchiectasis?

A. Cough with profuse expectoration of sputum, usually more marked in the morning after waking from sleep. Occasionally, hemoptysis and breathlessness in advance cases. Features of secondary infection may be present.

Q. What are the **typical signs of bronchiectasis?**

A. On general examination, there is generalized clubbing. On examination of the chest, there are coarse crepitations that reduce or disappear after coughing. The signs are usually better found on the back of the chest and are mostly basal.

Q. Why **hemoptysis?**

A. It is due to bronchial wall hypertrophy, hence mucosa becomes friable, slough out, capillary opens and bleeding occurs. Erosion of hypertrophic bronchial artery may result in massive hemoptysis.

Q. What is **dry bronchiectasis** (bronchiectasis sicca)?

A. It is a type of bronchiectasis in which dry cough is associated with intermittent episodes of hemoptysis. It may be massive, even life-threatening as bleeding is from bronchial vessels with systemic pressure. Common in patient with granulomatous infection, especially TB and usually involves upper lobe.

Q. What are the **characteristics of sputum** in bronchiectasis?

A. If the sputum is kept in a bottle, there are three layers:

- Lower sediment (epithelial debris and bacteria) layer
- Middle thick or liquid layer
- Upper frothy layer.

Q. What are the **causes** of basal crepitations?

A. As follows:

1. Unilateral basal crepitation:

- Unilateral bronchiectasis
- Resolution stage of pneumonia
- Lung abscess
- Localized fibrosis of lung.

2. Bilateral basal crepitation:
   - Bilateral bronchiectasis
   - IPF (fibrosing alveolitis or ILD)
   - Pulmonary edema.
3. Causes of bilateral crepitation with clubbing:
   - Bilateral bronchiectasis
   - IPF (fibrosing alveolitis or ILD).

Q. What is **post-tussive** crepitation? What is its **significance?**

A. Crepitation which appears after cough is called posttussive crepitation. It is usually at the apex, indicates TB.

Q. What **abnormalities** may be associated with bronchiectasis?

A. As follows:

- Situs inversus or dextrocardia and frontal sinusitis or agenesis (Kartagener's syndrome)
- Obstructive azoospermia and chronic sinopulmonary infection (Young's syndrome).

Q. What are the **complications** of bronchiectasis?

A. As follows:

- Secondary infection (pneumonia and pleurisy), common organisms are *Staphylococcus aureus*, *Haemophilus influenzae* and *Pseudomonas aeruginosa*
- Lung abscess
- Pleural effusion, empyema or pneumothorax
- Pulmonary hypertension and cor pulmonale
- Respiratory failure
- Amyloidosis (commonly involving spleen or kidney) in long standing case
- Brain abscess (metastatic cerebral abscess)
- Aspergiloma in the bronchiectatic cavity.

Q. How will you **treat** bronchiectasis?

A. As follows:

- Postural drainage, keeping the affected part remaining up and percussion over it. It is done for 5 to 10 minutes, once or twice daily
- Antibiotic, if infection
- Chest physiotherapy
- Surgery (lobectomy)
- Bronchodilator drugs. Also, nebulized salbutamol may be used in asthma, COPD, cystic fibrosis and ABPA
- Inhaled or oral steroid can decrease the rate of progression. Also, helpful in ABPA
- In bilateral extensive bronchiectasis, lung transplantation is required.

Indications of surgery: Usually in young patient. Indications are –

- Unilateral and localized to a single lobe or segment
- Severe and recurrent hemoptysis.

PLEURAL EFFUSION (TUBERCULAR)

CHIEF COMPLAINTS

- Cough with slight expectoration for … weeks
- Breathlessness for … days
- Fever for … days
- Weight loss for … days.

HISTORY

History of present illness: According to the statement of the patient, he was alright … weeks back. Since then, he has been suffering from frequent cough, which is present throughout day and night. The cough is usually dry with occasional slight expectoration of mucoid sputum, but no hemoptysis. He is also complaining of breathlessness, which is more marked during moderate to severe exertion, but there is no history of orthopnea or paroxysmal nocturnal dyspnea. The patient also complains of low grade continued fever for … days, more marked in the evening and associated with night sweats. During this period, he lost about 15 kg of body weight. There is no history of chest pain, joint pain or swelling, skin rash or any contact with patient with pulmonary TB. His bowel and bladder habits are normal.

History of past illness

Family history

Personal history

Socioeconomic history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient is ill-looking and emaciated
- Mildly anemic
- No jaundice, cyanosis, clubbing, edema, koilonychia or leukonychia
- No lymphadenopathy or thyromegaly
- Pulse: 100/min
- BP: 130/75 mm Hg
- Temperature: 100ºF
- Respiratory rate: 24/min.

SYSTEMIC EXAMINATION

Respiratory System: (Supposing Right Sided)

Inspection:

- Movement is restricted on lower part of right side of the chest with fullness of intercostal spaces
- (Mention, if any puncture mark, gauze and tape indicating aspiration of pleural fluid).

Palpation:

- Trachea is shifted to the left side

- Apex is shifted to the left (in 6th intercostal space in the anterior axillary line), normal in character
- Vocal fremitus is reduced in right lower chest up to … ICS (tell where)
- Chest expansion is restricted over the right lower chest.

Percussion:

- There is stony dullness in the right lower chest up to … ICS (tell where).

Auscultation:

- Breath sound—diminished (or absent) in the right lower chest
- Vocal resonance—diminished (or absent) in the right lower part of chest
- No added sound.

Note Just above the upper level of effusion, the following findings may be present (mention, if any)

- Bronchial sound
- Increased vocal resonance
- Whispering pectoriloquy
- Pleural rub.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 30 years, rickshawpuller, normotensive, nondiabetic, smoker, hailing from …, presented with frequent cough for … weeks, which is present throughout day and night. The cough is usually dry with occasional slight expectoration of mucoid sputum, but no hemoptysis. He is also complaining of breathlessness, which is more marked during moderate to severe exertion but there is no history of orthopnea or paroxysmal nocturnal dyspnea. The patient also complains of low grade continued fever for … days, more marked in the evening and associated with night sweats. During this period, he lost about 15 kg of body weight. There is no history of chest pain, joint pain or swelling, skin rash or any contact with patient with pulmonary TB. His bowel and bladder habits are normal. There is no history of such illness in his family.

He smokes 30 to 40 sticks per day for 15 years. He was treated by local physicians with antibiotic and paracetamol without any response.

On examination – general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is right sided pleural effusion.

Q. What is the **likely cause** of pleural effusion?

A. This is more likely to be tubercular, because:

- In the history, there is low grade fever with evening rise and night sweating
- Marked weight loss
- Cough with slight mucoid sputum.

Q. What may be the **other causes** in this case?

A. This may be due to:

- Post-pneumonic
- Lymphoma
- SLE (in female).

Q. Why not **bronchial carcinoma**?

A. The patient is young, bronchial carcinoma is less common (but he is a heavy smoker for 15 years, so carcinoma should be excluded.)

Q. Why not **thickened pleura?**

A. In this case, there is history of breathlessness, weight loss and fever which are not present in thickened pleura. Also, on examination, there is mediastinal shifting with stony dullness on the affected side. These are not found in thickened pleura.

Q. Why not **consolidation?**

A. There is stony dullness and reduced breath sound and vocal resonance in the affected area along with mediastinal shifting. These are against consolidation (In consolidation, there is woody dullness, bronchial breath sound, increased vocal resonance and no shifting of the mediastinum).

Q. Why not **collapse?**

A. In case of collapse, the apex beat and trachea will be shifted to the same side. In addition, if there is collapse with patent bronchus, there will be bronchial breath sound and increased vocal resonance**.**

Q. Why not **pneumothorax?**

A. In pneumothorax, there is hyper-resonance on percussion.

Q. What **investigations** do you suggest?

A. As follows:

1. X-ray chest P/A view
2. Hb%, TC, DC, ESR (high ESR in TB, leukocytosis in pneumonia)
3. Mantoux test (MT)
4. Aspiration of pleural fluid for analysis-
   - Physical appearance (straw colored, serous, hemorrhagic, chylous)
   - Gram-staining, cytology (routine) and exfoliative cytology (malignant cells)
   - Biochemistry (protein and sugar), also a simultaneous blood sugar, protein and lactate dehydrogenase (LDH) may be done
   - ADA (high in tuberculosis)
   - Culture and sensitivity (C/S)
   - AFB and mycobacterial C/S
5. Pleural biopsy by Abram's or Cope's needle
6. Other investigation of pleural fluid (according to suspicion of cause):
   - Cholesterol, LDH and rheumatoid factor (in rheumatoid arthritis)
   - Amylase (high in acute pancreatitis, esophageal rupture, malignancy)
   - Trigycerides (in chylothorax)
7. Sputum (if present) for Gram staining, C/S, AFB, mycobacterial C/S and malignant cells (exfoliative cytology)
8. If palpable lymph node: FNAC or biopsy (for lymphoma, metastasis)
9. Other investigations according to suspicion of causes include:
   - ANF, anti-ds DNA (SLE)
   - Liver function tests
   - Urine for protein and serum total protein (nephrotic syndrome)
   - CT scan in some cases (it helps to clarify pleural abnormalities more readily than chest X-ray and ultrasonogram, and also helps to distinguish between benign and malignant diseases).

Note

In tuberculosis, AFB is positive in pleural fluid in 20% cases and pleural biopsy is positive in 80% cases. In malignancy, pleural biopsy is positive in 40% cases (may be up to 60% cases).

RELATED QUESTIONS AND ANSWERS

Q. What is **pleural effusion?**

A. Accumulation of excessive amount of fluid in pleural cavity is called pleural effusion.

Q. What are the **definitive signs** of pleural effusion?

A. Stony dullness on percussion and reduced or absent breath sound (confirmed by aspiration).

Q. How to **confirm** if there is small effusion? (if not detected by chest X-ray PA view.)

A. By doing:

- X-ray in lateral decubitus position
- Ultrasonogram (USG) of lower part of the chest
- Occasionally, CT scan of chest may be needed.

Q. What are the **characteristics** of pleuritic chest pain?

A. Pleuritic chest pain is localized, sharp or lancinating in nature, worse on coughing, deep inspiration or movement.

Q. **What are the causes of** dullness on percussion **over lower chest?**

A. As follows:

- Pleural effusion (stony dullness)
- Thickened pleura
- Consolidation (woody dullness)
- Collapse of the lung
- Raised right hemidiaphragm (due to hepatomegaly or liver pushed up)
- Mass lesion.

Note Remember the following points in pleural effusion:

- Pleural fluid normally present: 5 to 15 mL
- At least 500 mL of fluid is necessary to detect clinically
- At least 300 mL of fluid is necessary to detect radiologically in PA view
- At least 100 mL of fluid is necessary to detect radiologically in lateral decubitus position
- Less than 100 mL or small amount of fluid is detected by ultrasonography (even 20 to 25 mL fluid can be detected).

Q. Supposing, clinically it is pleural effusion but **no fluid** is coming after aspiration. What are the **possibilities?**

A. As follows:

- Fluid may be thick (empyema)
- Thickened pleura
- Mass lesion.

Q. What are the common causes of pleural effusion?

A. Four common causes are:

- Pulmonary tuberculosis
- Parapneumonic (also called postpneumonic)
- Bronchial carcinoma
- Pulmonary infarction.

If the patient is young, common causes are

- Pulmonary tuberculosis
- Parapneumonic
- Others—Lymphoma and SLE in female (also pulmonary infarction).

If the patient is middle age or elderly, common causes are:

- Pulmonary tuberculosis
- Parapneumonic
- Bronchial carcinoma.

Q. What are the causes of predominantly **right** or **left** sided pleural effusion?

A. As follows:

Causes of right-sided pleural effusion

- Liver abscess
- Meig's syndrome
- Dengue hemorrhagic fever.

Causes of left-sided pleural effusion

- Acute pancreatitis
- Rheumatoid arthritis
- Dressler's syndrome
- Esophageal rupture (Boerhaave's syndrome)
- Dissecting aneurysm.

Q. What are the causes of bilateral effusion?

A. **As follows:**

- All causes of transudative effusion (CCF, nephrotic syndrome, cirrhosis of liver, malabsorption or malnutrition or hypoproteinemia).
- Collagen diseases (rheumatoid arthritis and SLE).
- Lymphoma.
- Bilateral extensive pulmonary TB.
- Pulmonary infarction.
- Malignancy (usually multiple metastases involving both lungs).

Q. What are the **causes** of exudative and transudative pleural effusion?

A. As follows:

1. **Exudative** (protein **>3 g%**)**:**
   - Pulmonary tuberculosis
   - Pneumonia
   - Bronchial carcinoma
   - Pulmonary infarction
   - Collagen disease (SLE, rheumatoid arthritis)
   - Lymphoma.

- Dressler's syndrome (post-myocardial infarction syndrome characterised by pain, pyrexia, pericarditis, pleurisy and pneumonitis).
- Others—acute pancreatitis, subphrenic abscess, liver abscess, pleural mesothelioma, secondaries in the pleura, yellow nail syndrome, etc.

2. **Transudative** (protein **<3 g%**):
   - Congestive cardiac failure (CCF)
   - Nephrotic syndrome
   - Cirrhosis of liver
   - Malnutrition
   - Hypothyroidism
   - Meig's syndrome (ovarian fibroma, ascites and right sided pleural effusion)
   - Chronic constrictive pericarditis
   - Acute rheumatic fever.

Q. How to **differentiate** between exudative and transudative pleural effusion?

A. As follows:

Criteria	Exudative	Transudative
1. Appearance	Straw, purulent, hazy, chylus or blood-stained	Clear or serous
2. Protein	>3 g%	<3 g%
3. Glucose	Low	Normal
4. Cholesterol	> 60 mg/dL	< 60 mg/dL
5. LDH	> two thirds of the upper limit of normal serum LDH	< two thirds of the upper limit of normal serum LDH
6. Pleural fluid LDH : serum LDH	>0.6	<0.6
7. Pleural fluid protein : serum protein	>0.5	<0.5
8. Serum-effusion albumin gradient (serum albumin minus pleural fluid albumin)	< 1.2 g/dL	>1.2 g/dL

Note Remember the following:

- Pleural fluid cholesterol level < 60 mg/dl indicates transudate. In all malignant effusion, pleural fluid cholesterol > 60 mg/dL. So, this test is useful to separate these two types of effusion.
- High pleural fluid ADA indicates tubercular pleural effusion.

Q. What are the **types** of pleural effusion according to the color?

A. According to color, pleural effusion may be:

- Serous (hydrothorax)
- Straw
- Purulent (empyema or pyothorax)
- Hemorrhagic (hemothorax)
- Milky or chylous (chylothorax)

Note

Clinically, only pleural effusion should be mentioned. After drawing the fluid and according to its color, other diagnosis may be done. e.g. if pus, it is empyema.

Q. What are the causes of **hemothorax (blood stained fluid)?**

A. As follows:

- Chest injury or trauma
- Bronchial carcinoma
- Pleural mesothelioma
- Pulmonary infarction
- Others – SLE, lymphoma, acute pancreatitis.

Q. What are the **differences** between traumatic hemothorax and hemorrhagic pleural effusion?

A. As follows:

Traumatic hemothorax	Hemorrhagic pleural effusion
1. Less uniform	1. Uniformly mixed
2. Usually clots on standing	2. Does not clot
3. Gross hemorrhage, RBC >100,000/mm^3	3. RBC > 10,000/mm^3
4. RBC not crenated (fresh RBC)	4. RBC may be crenated

Q. What are causes of **empyema?**

A. As follows:

- Bacterial pneumonia
- Lung abscess (bursting in pleural cavity)
- Bronchiectasis
- Tuberculosis
- Secondary infection after aspiration
- Rupture of subphrenic abscess or liver abscess
- Infected hemothorax.

Q. How to diagnose **empyema thoracis** clinically?

A. As follows:

From history:

- High fever, sometimes hectic, may be associated with chill, rigor and sweating. Fever is persistent or recurrent despite treatment with a suitable antibiotic.
- Malaise, weight loss.
- Pleuritic chest pain, breathlessness.
- Copious purulent sputum if empyema rubtures into a bronchus (bronchopleural fistula).

On examination:

- Toxic, emaciated.
- Tachypnea.
- Tachycardia.
- Features of pleural effusion.
- Clubbing.
- To be confirmed—aspiration which shows pus or purulent fluid.

Q. What is empyema necessitans?

A. In empyema thoracis, fluid may come out subcutaneously in the chest wall. This is called empyema necessitans.

Characteristics of empyema fluid:

- Fluid is purulent
- Thick
- Biochemical—glucose low, < 3.3 mmol/L, protein exudative, LDH > 1000 U/L
- C/S—organism may be found
- Pleural biopsy may be done to exclude tuberculosis.

Q. How to treat empyema thoracis?

A. According to cause:

1. Non-tuberculus:
   - Drainage of pus with wide bore intercostal tube using water seal drainage.
   - Antibiotic for 2 to 6 weeks. IV Co-amoxiclav or cefuroxime plus metronidazole. May be given according to C/S.
   - Surgical intervention if pus is thick or loculated. Surgical decortication of the lung may be needed, if visceral pleura is grossly thickened.
2. Tuberculous empyema:
   - Antitubercular drug
   - Wide bore needle aspiration or intercostal tube drainage
   - Sometimes surgical ablation of pleura.

Q. What are causes of chylothorax (milky or whitish fluid due to lymph)?

A. Injury or obstruction of thoracic duct due to any of the following causes:

- Traumatic (surgery and trauma to the thoracic duct)
- Neoplastic (bronchial carcinoma and metastasis)
- Infective (tuberculosis and filariasis)
- Lymphoma involving thoracic duct.

Q. How to differentiate between chylothorax and empyema?

A. In both cases, fluid may be cloudy. It is centrifuged and following is observed:

- If clear, empyema
- If persistent cloudy or milky, chylothorax.

Q. What is hydrothorax? How to diagnose it clinically?

A. When the pleural effusion is transudative, it is called hydrothorax. It is usually bilateral due to any cause causing transudative pleural effusion.

Clinically this can be diagnosed by:

- Presence of primary cause like CCF, nephrotic syndrome, cirrhosis of liver, etc.
- Associated edema which may be generalized, also ascites, pericardial effusion.
- No history of fever or acute infection.
- Aspiration of fluid shows transudative in nature (serous in color and protein < 3 g%).

Q. What are the causes of recurrent pleural effusion? How to treat recurrent pleural effusion?

A. As follows:

- Bronchial carcinoma
- Pleural mesothelioma

- Lymphoma
- Collagen disease (SLE)
- All causes of transudate (CCF, nephrotic syndrome, cirrhosis of liver).

Treatment of recurrent pleural effusion is done by pleurodesis in the following way:

- A plain rubber tube is introduced in the intercostal space, and fluid is removed as far as possible. Introduce the drug, tetracycline (500 mg) or kaolin or talc through the tube, clamp it and keep for 4 to 8 hours (may be overnight). In malignant pleural effusion, bleomycin 30 to 60 mg is introduced.
- Patients' posture should be changed 2 hourly to allow the drug to spread in pleural space.
- After 4 to 8 hours, remove any remaining fluid and take out the drainage tube at the height of inspiration.
- The patient usually complains of severe chest pain after pleurodesis. In such case, analgesic should be given.

Q. How can you suspect malignant effusion?

A. As follows:

- Clincally—elderly emaciated or cachexic patient having clubbing with nicotine stain, palpable lymph node, radiation mark on the chest, etc.
- Pleural fluid is hemorrhagic and there is rapid accumulation after aspiration.

Q. What are causes of high eosinophil in the pleural fluid (also high in the blood)?

A. As follows:

- Pulmonary eosinophilia
- Polyarteritis nodosa
- Rarely lymphedema.

Note

High eosinophil in the pleural fluid but not in the blood is likely due to pulmonary embolism. High eosinophil in pleural fluid is unlikely to be malignant.

Q. What is subpulmonary pleural effusion?

A. Effusion between the lower surface of lung and upper surface of diaphragm. Confused with subphrenic abscess. Detected by chest X-ray in lateral decubitus position or USG or CT scan.

Q. What is pseudotumor (phantom tumor)?

A. It is the accumulation of fluid in interlobular fissure, usually found along the lateral chest wall. Chest X-ray shows rounded homogeneous opacity, misdiagnosed as a tumor. It is confirmed by USG (localized or encysted effusion) or CT scan. It disappears with resolution of effusion. It is commonly found in CCF.

Q. What is yellow nail syndrome?

A. It is a congenital disorder characterized by:

- Nails—yellow, thick, onycholysis
- Lymphedema of legs
- Pleural effusion or bronchiectasis.

Q. What are the mechanisms of pleural effusion?

A. Excess pleural fluid accumulation occurs when pleural fluid formation exceeds absorption or normal pleural fluid formation with reduced absorption. Probable mechanisms are:

- Increased hydrostatic pressure (as in CCF)

- Reduced plasma colloidal osmotic pressure (as in hypoproteinemia)
- Involvement of pleura causing increased permeability (as in TB and tumor)
- Impaired lymphatic drainage of pleural space (as in obstruction of lymphatic system by tumor, TB and radiation)
- Transdiaphragmatic passage of fluid (in liver disease, ascites and acute pancreatitis).

Q. What is the **mechanism** of tuberculous pleural effusion?

A. Hypersensitivity to tuberculous protein in pleural space.

Q. What are the **characteristics** of tuberculous pleural effusion?

A. As follows:

- Straw or amber color
- Exudative
- High lymphocyte in pleural fluid
- AFB is found in 20% cases
- Culture for AFB is found in one-third cases
- Pleural biopsy is positive in 80% cases.

Q. What are the causes of **low pH and low glucose** in pleural fluid?

A. As follows:

- Infection (empyema)
- Tuberculosis
- Advanced malignancy
- SLE
- Rheumatoid arthritis
- Esophageal rupture.

Q. What is the role of **pleural fluid amylase?**

A. Pleural fluid amylase may be higher than serum amylase in acute pancreatitis, bacterial pneumonia, esophageal rupture and malignancy. It is high in adenocarcinoma of lung and may be useful in differentiating it from mesothelioma.

Q. What is the **treatment** of pleural effusion?

A. Treatment should be according to cause. For example:

- If tuberculosis: Full course antitubercular therapy. Prednisolone 20 to 30 mg daily may be given for 4 to 6 weeks, especially in large effusion.
- If parapneumonic: Aspiration of fluid, may be repeated if necessary. Antibiotic should be given. If complicated case, especially empyema, thoracostomy may be done. Sometimes, if all fails, thoracotomy with decortication may be necessary.

Q. **How much fluid** may be drawn at a time?

A. Usually up to 1500 mL. If more is drawn, there may be risk of re-expansion pulmonary edema. The mechanism is because of effusion, lung is compressed and there is ischemia to lung parenchyma and necrosis of pulmonary vessels. If more fluid is drawn, there is rapid expansion of the lung, as no regeneration of necrotic vessels. As a result, more leakage of fluid causing pulmonary edema.

Q. What is the role of **steroid** in pleural effusion?

A. Steroid is mostly given in tubercular pleural effusion. Although its role is controversial, some evidences suggest that it promotes rapid absorption of pleural fluid and gives the patient quick symptomatic relief. It also prevents pleural fibrosis and adhesion. Steroid should be used along with antitubercular therapy.

LUNG ABSCESS

CHIEF COMPLAINTS

- Cough with profuse foul smelling sputum for … days
- Hemoptysis for … days
- Fever for … days
- Chest pain for … days
- Malaise, weakness, loss of weight for … days.

HISTORY

History of present illness: According to the statement of the patient, he was reasonably well … days back. Since then, he has been suffering from severe cough with production of copious foul smelling purulent sputum. It is occasionally associated with scanty amount of blood. He also complains of high grade continuous fever, highest recorded 104°F. The fever is associated with chills and rigors and profuse sweating, subsides only with paracetamol. The patient also complains of right sided chest pain, which is compressive in nature, worse with inspiration and during coughing, but there is no radiation. For the last ... days, he is also suffering from malaise, weakness, anorexia and loss of approximately 15 kg of body weight. His bowel and bladder habits are normal.

History of past illness: He was suffering from pneumonia 6 months back from which there is complete recovery.

Family history: Nothing significant.

Personal history: He smokes about 25 sticks a day for 25 years. He is also an alcoholic.

Socioeconomic history: He is a day laborer and lives in a slum area with poor sanitation.

Drug history: The patient was treated by local physicians with antibiotics, cough syrup and paracetamol, but no improvement.

GENERAL EXAMINATION

- The patient looks toxic and emaciated
- Generalized clubbing is present in all the fingers and toes
- Moderately anemic
- No jaundice, cyanosis, koilonychia, leukonychia or edema
- No thyromegaly or lymphadenopathy
- Pulse: 110/min
- BP: 110/75 mm Hg
- Temperature: 103º F
- Respiratory rate: 28/min.

SYSTEMIC EXAMINATION

Respiratory System

(Supposing right sided)

Inspection:

- Movement is restricted in the right side of the chest.

Palpation:
- Trachea is central in position
- Apex beat is in the left 5th intercostal space in the midclavicular line
- Vocal fremitus is increased on the right side of the chest
- Chest expansion is reduced on the right side.

Percussion:
- Percussion note is woody dull over right side of chest from … to … intercostal space
- Upper border of the liver dullness is in the right 5th intercostal space in midclavicular line
- Cardiac dullness is normal.

Auscultation:
- Breath sound is bronchial in … intercostal space on the right side. In other places, it is vesicular.
- Vocal resonance is increased over the same area.
- There are coarse crepitations over the right side of the chest in … intercostal space, reduces on coughing.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mr. …, 42 years old, day laborer, normotensive, nondiabetic, smoker and alcoholic, hailing from …, presented with severe cough with production of copious foul smelling purulent sputum for … days. It is occasionally associated with scanty amount of blood. He also complains of high grade continuous fever, highest recorded 104°F. The fever is associated with chills and rigors and profuse sweating, subsides only with paracetamol. The patient also complains of right sided chest pain, which is compressive in nature, worse with inspiration and during coughing, but there is no radiation. For the last ... days, he is also suffering from malaise, weakness, anorexia and loss of approximately 15 kg of body weight. His bowel and bladder habits are normal. He was suffering from pneumonia 6 months back from which there is complete recovery. He smokes about 25 sticks a day for 25 years. He was treated by local physicians with antibiotics, cough syrups and paracetamol, but no improvement.

On examination—general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is right sided lung abscess.

Q. What are the **differential diagnoses**?

A. As follows:
- Consolidation (during resolution stage)
- Bronchiectasis
- Bronchial carcinoma
- Pulmonary TB.

Q. Why lung abscess and **not** consolidation?

A. Because:
- The patient is toxic with high temperature. There is cough with foul smelling purulent sputum.
- Clubbing is present (it is usually present in 10% cases after 3 weeks.)

To be confirmed—chest X-ray should be done (which shows cavity with air fluid level).

Q. With these findings, can it be **consolidation** only?

A. Yes, it may be during resolution stage.

Q. Could it be **bronchiectasis?**

A. Yes, because there is clubbing with coarse crepitations. However, in bronchiectasis, crepitations are mostly on the basal area. Also, there is no fever and patient is not toxic in bronchiectasis (until there is secondary infection).

Also, in the history of bronchiectasis, there is profuse expectoration of sputum after waking up from sleep in the morning.

Q. **What** investigations **should be done in lung abscess?**

A. As follows:

- CBC (leukocytosis)
- X-ray chest (cavity with air fluid level)
- Sputum examination—Gram staining, C/S (both aerobic and anaerobic), AFB, fungus, malignant cells
- Bronchoscopy (to exclude mass and foreign body)
- CT or MRI (in some cases)
- Blood sugar.

RELATED QUESTIONS AND ANSWERS

Q. What is **lung abscess?** What are the **causes?**

A. It is a localized area of suppuration within the lung parenchyma that leads to parenchymal destruction and is manifested radiologically as a cavity with air fluid level.

Causes of lung abscess:

- Aspiration of nasopharyngeal or oropharyngeal contents, such as in vomiting, anesthesia, tooth extraction, tonsillectomy, unconscious patient, alcoholism and achalasia of cardia. Organisms are aerobic and anaerobic.
- Specific infections (*Streptococcus pneumoniae* type 3, *Staphylococcus aureus, Klebsiella pneumoniae* and fungal). In HIV, *Pneumocystis jiroveci, Cryptococcus neoformans* and *Rhodococcus equi.*
- Obstruction by bronchial carcinoma, adenoma and foreign body.
- Infection in pulmonary infarction (by *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae* and anaerobic).
- Spread from liver abscess and subphrenic abscess (due to transdiaphragmatic spread).
- Hematogenous from other infection as septic emboli (pelvic abscess and salpingitis, right sided endocarditis, IV drug abuse).

Q. How the patient of lung abscess usually **presents?**

A. As follows

- Severe cough with profuse foul smelling sputum, may be fetid (anaerobic)
- Hemoptysis
- Chest pain (pleuritic)
- Fever, usually high with chill and rigor, with profuse sweating
- Malaise, weakness and loss of weight.

Q. What are the **physical findings** in lung abscess?

A. It depends on site. If deep seated within the lung parenchyma, there may not be any physical findings. If it is near the surface, findings are:

- Features of consolidation, usually

- Rarely, features of cavitation
- Sometimes, combined features of consolidation and cavitation, if large abscess.

Q. What is the **common site** of lung abscess?

A. As follows:

1. Lung abscess is common in right middle lobe.
2. If it is due to aspiration, then the commonest site depends on the posture of the patient during aspiration.
   - If the patient is lying down, abscess forms in the posterior segment of upper lobe or superior segment of lower lobe
   - If the patient is in upright position, the common site is basal segment.

Q. Why lung abscess is more common on the **right side**?

A. Lung abscess is more common in right side due to less obliquity of the right major bronchus.

Q. What are the **complications** of lung abscess?

A. As follows:

- Pleurisy
- Empyema
- Bronchiectasis
- Fibrosis
- Septicemia
- Cerebral abscess (common in parietal lobe or posterior frontal region)
- Amyloidosis (rare), in chronic cases.

Q. What are the **characteristics of sputum** in lung abscess?

A. If the sputum is kept in a bottle, there are three layers (as in bronchiectasis):

- Lower—sediment (epithelial debris and bacteria)
- Middle—thick liquid
- Upper—frothy.

Q. What are the other causes of **cavitary lesion in lung?**

A. As follows:

- Tuberculosis
- Cavitating bronchial carcinoma
- Pulmonary infarction
- Fungal infection (histoplasmosis)
- Wegener's granulomatosis
- Rheumatoid nodules
- Consolidation (*Streptococcus pneumoniae* serotypes 3).

Q. What are the causes of **multiple cavitary lesions** in the lung?

A. As follows:

- Tuberculosis
- Staphylococcal lung abscess (in children)
- Fungal infection
- Klebsiella
- Amebiasis.

Q. What are the causes of **multiple lung abscess**?

A. As follows:

- Aspiration of infected material
- *Staphylococcus aureus* (in children)
- Klebsiella infection
- Fungal infection
- Amebiasis.

Q. How to **treat** lung abscess?

A. Sputum is sent for C/S and broad-spectrum antibiotic should be started.

- Broad-spectrum antibiotic—amoxicillin or co-amoxiclav or erythromycin **plus** metronidazole. **Or,** cefuroxime 1 g IV 6 hourly **plus** metronidazole 500 mg IV 8 hourly for 5 days, followed by cefaclor **plus** metronidazole (in 70% cases anaerobic organisms are present, but mixed organisms are also common).
- If improves, continue as above. If no response, antibiotic is given according to C/S. Treatment should be continued for 4 to 6 weeks.
- Postural drainage and chest physiotherapy.
- If no response to medical therapy (occurs in 1 to 10% cases), percutaneous aspiration (USG or CT guided).
- Sometimes, surgery (lobectomy) may be done.
- Treatment of the cause, if present.

Indications of surgery:

- No clinical response
- Increasing size of the abscess.
- Massive hemorrhage or hemoptysis.

BRONCHIAL CARCINOMA

CHIEF COMPLAINTS

- Cough with expectoration for … months
- Occasional haemoptysis for … months
- Chest pain for … days
- Weight loss, malaise, weakness, loss of appetite for … days.

HISTORY

History of present illness: The patient was alright … months back. Since then, he has been suffering from frequent cough, which is present throughout the day and night. The cough is usually dry, sometimes associated with slight mucoid sputum expectoration. Occasionally, the patient noticed streaks of frank blood with sputum during coughing. There is one episode of massive hemoptysis … days back. For the last … days, he is also complaining of right sided chest pain, which becomes worse with deep inspiration, coughing and also on lying down on right side. The patient also complains of loss of appetite, substantial loss of weight, weakness and malaise for ... days. His bowel and bladder habits are normal. There is no history of fever, hoarseness of voice, difficulty in deglutition, contact with TB patients.

History of past illness: Nothing significant.

Family history: Nothing contributory.

Personal history: He smokes about 25 sticks per day for 30 years.

Socioeconomic history: He is a clerk and comes from a middle class family.

Drug history: He used to take some cough syrup and occasionally antibiotics, the name of which he cannot mention.

GENERAL EXAMINATION

- Ill-looking and emaciated
- Moderately anemic
- Generalized clubbing present involving all the fingers and toes (mention hypertrophic osteoarthropathy is present or not)
- Nicotine stain present in right finger nail (mention if any)
- Right supraclavicular lymph nodes are enlarged, hard in consistency, nontender, fixed with underlying structure and overlying skin
- No jaundice, cyanosis, edema, koilonychias or leukonychia
- No thyromegaly
- Pulse: 84/min
- BP: 110/70 mm Hg
- Respiratory rate: 20/min
- Temperature: Normal.

SYSTEMIC EXAMINATION

Respiratory System

(Supposing right sided)

Inspection:

- Movement is restricted on right upper chest
- There is radiation mark on the chest (if any).

Palpation:

- Trachea is central in position
- Apex beat is in left 5th intercostal space, just medial to the midclavicular line
- Vocal fremitus is reduced (or absent) in right upper chest
- Pleural rub is present (mention where).

Percussion:

- Percussion note is dull in right upper chest (mention up to which space)
- Upper border of the liver dullness is in the right 5th intercostal space in the midclavicular line
- Cardiac dullness is normal.

Auscultation:

- Breath sound is reduced (or absent)
- Vocal resonance is reduced (or absent)
- Few crepitations (may be present)
- Pleural rub is present (mention where).

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 52 years old, a clerk, normotensive, nondiabetic, smoker, hailing from …, presented with frequent cough for … months, which is present throughout the day and night. The cough is usually dry, sometimes associated with slight mucoid sputum expectoration. Occasionally, the patient noticed streaks of frank blood with sputum during coughing. There is one episode of massive hemoptysis … days back. For the last … days, he is also complaining of right sided chest pain, which becomes worse with deep inspiration, coughing and also on lying down on right side. The patient also complains of loss of appetite, substantial loss of weight, weakness and malaise for ... days. His bowel and bladder habits are normal. There is no history of fever, hoarseness of voice, difficulty in deglutition, contact with TB patients. He smokes about 25 sticks a day for the last 30 years. He used to take some cough syrup and occasionally antibiotics, the name of which he cannot mention.

On examination – general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is bronchial carcinoma with metastasis (in right supracalvicular LN).

Q. Why **bronchial carcinoma?**

A. The patient is elderly and heavy smoker. There is history of cough with hemoptysis and marked loss of weight. On examination, the patient is emaciated, has generalized clubbing with nicotine stain and examination of chest shows evidence of mass lesion. All the features are suggestive of bronchial carcinoma.

Q. What are your differential diagnoses?

A. As follows:

- Pulmonary TB
- Other mass lesion (hydatid cyst, dermoid cyst, neurofibroma).

Q. Why pulmonary TB is not your primary diagnosis?

A. This may be pulmonary tuberculosis, because all the features like cough, hemoptysis and weight loss are present in tuberculosis. However in this case, there is no history of fever or contact with TB patient. The patient has gross clubbing, enlarged supraclavicular lymph node, which is hard in consistency and evidence of mass lesion in chest. All these are against pulmonary tuberculosis.

Q. Why not this is collapse?

A. In collapse, trachea and apex beat are shifted to the same side.

Q. Why not consolidation?

A. In consolidation, there is bronchial breath sound and increased vocal resonance.

Q. What investigations do you suggest in bronchial carcinoma?

A. **As follows:**

1. X-ray chest P/A view (homogeneous irregular opacity, with **sun-ray** appearance may be seen. There may be collapse, pleural effusion, hilar lymphadenopathy, widening of mediastinum, raised hemidiaphragm, and rib erosion or destruction).
2. Sputum for malignant cells (exfoliative cytology).
3. CT scan of chest (MRI is not helpful for primary lesion).
4. CT guided FNAC.
5. FNAC (or biopsy) of lymph nodes (if present).
6. Fiber optic bronchoscopy and biopsy (or bronchial washing and brushing).
7. PET-CT scan is the investigation of choice (highly sensitive and specific for mediastinal staging).
8. To see evidence of metastasis: USG of whole abdomen, X-ray skull, isotope bone scan, etc. Sometimes, CT scan of chest and abdomen, even MRI may be needed.
9. Others:
   - Complete blood count, ESR
   - If pleural effusion, then fluid cytology. Pleural biopsy may also be done
   - Liver function test, renal function test (before chemotherapy, if needed)
   - Pulmonary function test specially FEV_1 (DLCO below 60% predicted is associated with a mortality rate of 25% due to pulmonary complications).

Q. Why bronchoscopy should be done?

A. Bronchoscopy should be done:

- To see the mass and to take biopsy for tissue diagnosis. This will guide further management.
- If the carcinoma involves first 2 centimeter of either main bronchus, it indicates the tumor is inoperable.
- If carina is wide and there is loss of sharp angle of carina, it indicates presence of enlarged madiastinal lymph nodes (may be malignant or reactive). Biopsy can be taken by passing a needle through bronchial wall.
- Vocal cord paralysis on the left indicates left recurrent laryngeal nerve palsy and indicates an inoperable case.

Q. Have you examined the eyes of the patient? What did you look for?

A. I have examined the eyes for partial ptosis, miosis and enophthalmos, which indicates Horner's syndrome. It is commonly found in Pancoast's tumor. Fundoscopy may show papilledema, if secondary metastasis in the brain.

Q. If **sputum** shows malignant cells, would you do **bronchoscopy** and **biopsy**?

A. Yes, to see histological type. This is helpful for therapy and prognosis. If squamous cell carcinoma, radiotherapy is the treatment. If small cell carcinoma, chemotherapy is necessary.

RELATED QUESTIONS AND ANSWERS

Q. What are the **types** of bronchial carcinoma?

A. Two types:

- Non-small-cell carcinoma in 80%
- Small-cell carcinoma in 20%.

Q. What are the **histological types** of bronchial carcinoma?

A. Four types:

- Squamous cell carcinoma in 35%
- Small cell carcinoma in 20%
- Adenocarcinoma in 30%
- Large cell carcinoma in 15%.

Features of adenocarcinoma:

- Ten percent of bronchial carcinoma
- Arises from mucous cells in the bronchial epithelium
- Occurs in the periphery of lung
- Usually develops in or around old scar
- More in elderly
- More in female
- More in nonsmokers
- More in far east
- More in asbestosis
- Invasion to pleura and mediastinal lymph nodes is common
- Metastasis to brain, bone and adrenal gland is common.

Features of small cell carcinoma:

- About 20 to 30% of bronchial carcinoma
- Arises from endocrine cells called Kulchitsky cells. These cells are members of APUD system, which secretes many polypeptide hormones. Some of these hormones act in an autocrine fashion, they feedback on the cells and cause cell growth
- Highly malignant, rapidly growing, early metastasis and inoperable at presentation
- Usually responds to chemotherapy and radiotherapy, less likely to be cured by surgery
- Overall prognosis is poor. Survival is short, 3 months to 1 year.

Features of bronchoalveolar cell carcinoma:

- Found in 1 to 2% of bronchial carcinoma
- Occurs as peripheral solitary nodule or diffuse nodular lesion of multicentric origin
- It may be associated with profuse mucoid sputum expectoration.

Q. What are the **causes or risk factors** of bronchial carcinoma?

A. As follows:

- Cigarette smoking is the major risk factor. Even passive smoking causes 1.5 times increase in the risk of bronchial carcinoma.
- Other factors are exposure to asbestos, silica, beryllium, cadmium, chromium, arsenic, iron oxide, radon, radiation, petroleum products and oils, coal tar, products of coal combustion.
- Adenocarcinoma may develop in nonsmokers and in old scar.

Q. What are the **presentations** of bronchial carcinoma?

A. Usually in elderly patients with history of smoking:

1. Due to lung lesion:
- Cough—dry or sputum production. Changing pattern of regular cough in a smoker is highly suspicious. Bovine cough due to left recurrent laryngeal nerve palsy.
- Hemoptysis, commonly in central lesion. Sometimes, involvement of large blood vessels causes massive hemoptysis.
- Breathlessness (due to bronchial obstruction, collapse or massive pleural effusion or compression of phrenic nerve causing paralysis of the diaphragm).
- Chest pain (due to involvement of pleura, rib or chest wall, intercostal nerve and brachial plexus).
- Recurrent pneumonia at the same site or pneumonia with slow resolution is highly suspicious.
- Apical tumor (called Pancoast's tumor) involves cervical sympathetic chain at or above the stellate ganglia, causing Horner's syndrome (characterized by ipsilateral partial ptosis, enophthalmos, miosis and anhydrosis of the face). Also, there is pain in shoulder and inner aspect of arm due to the involvement of lower trunk of brachial plexus, called Pancoast's syndrome.

2. Due to local spread in mediastinum:
- Hoarseness of voice and a bovine cough (due to involvement of left recurrent laryngeal nerve by left hilar lesion).
- Dysphagia (esophageal obstruction, also cardiac tamponade).
- SVC obstruction (with right sided mass or mediastinal lymphadenopathy).
- If pericardium is invaded, there may be pericardial effusion or arrhythmia.
- Stridor, when lower trachea, carina and main bronchi are narrowed by primary tumor or compression by subcarinal and paratracheal lymph nodes.

3. Distant metastasis (in liver, brain, bone, adrenal, contralateral lung and lymph nodes. Metastatic features usually common in adenocarcinoma).

4. Nonmetastatic extrapulmonary manifestations (see below).

5. General features of malignancy—anorexia, weight loss, malaise, fatigue.

Q. Why **chest pain** in bronchial carcinoma?

A. Due to metastasis in the rib or chest wall invasion.

Q. What is **Pancoast's tumor** and **Pancoast's syndrome**?

A. As follows:
- Pancoast's tumor (superior sulcus tumor): It is the tumor that arises from apex of the lung. It may involve the cervical sympathetic chain, causing Horner's syndrome.
- Pancoast's syndrome**:** This is characterized by pain in the shoulder or inner aspect of arm along the ulnar nerve distribution due to the involvement of lower part of brachial plexus (C_8, T_1 and T_2). There may be wasting of small muscles of hand due to C_8 and T_1 nerve involvement. Local invasion by the tumor may cause pain and tenderness of the first and second ribs with evidence of rib destruction radiologically. Horner's syndrome may occur due to involvement of the sympathetic pathway as it passes through T_1 root. In Pancoast's syndrome, treatment is by combined surgery and radiotherapy.

Non-metastatic extra-pulmonary manifestations (paraneoplastic syndrome) -

Occur in 15 to 20% cases of bronchial carcinoma due to secretory products by the tumor. These may precede, coincide or follow after the cancer. Treatment of carcinoma improves the features.

1. Endocrine (10%, usually in small cell carcinoma):
   - SIADH (syndrome of inappropriate ADH, usually in small cell carcinoma)
   - ACTH secretion causing Cushing's syndrome (usually in small cell carcinoma)
   - Carcinoid syndrome (usually in small cell carcinoma)
   - Hypercalcemia due to release of parathormone-like substance (usually in squamous cell carcinoma)
   - Gynecomastia due to excess estrogen (in large cell)
   - Rarely, hypoglycemia and thyrotoxicosis.
2. Neurological (in any type):
   - Peripheral neuropathy (usually sensorimotor)
   - Cerebellar degeneration
   - Cortical degeneration (dementia)
   - Myelopathy—motor neuron disease like feature
   - Retinal blindness (small cell carcinoma).
3. Musculoskeletal:
   - Polymyositis or dermatomyositis (in all types)
   - Myasthenic myopathic syndrome (Eaton-Lambert syndrome)
   - Clubbing and hypertrophic osteoarthropathy (non-small-cell type).
4. Hematological (in all types):
   - Migrating thrombophlebitis
   - DIC
   - Thrombotic thrombocytopenic purpura
   - Normocytic normochromic anemia and occasionally, hemolytic
   - Eosinophilia.
5. Heart (in adenocarcinoma):
   - Marantic endocarditis (non-bacterial, thrombotic or verrucous endocarditis).
6. Skin (in all types):
   - Acanthosis nigricans
   - Dermatomyositis
   - Herpes zoster.
7. Renal:
   - Nephrotic syndrome due to membranous glomerulonephritis (rare).
8. Metabolic (universal at some stage):
   - Loss of weight
   - Lassitude
   - Anorexia.

Q. How to **treat** bronchial carcinoma?

A. As follows:

1. Non-small-cell carcinoma:
- Surgery should be done, if the tumor is localized to lobe or segment. (It is curative if the stage is T1N0M0)
- If surgery is not possible, radiotherapy or chemotherapy or combined therapy should be given.
- In squamous cell type, radiotherapy is advised (it is especially indicated in SVC obstruction, repeated hemoptysis and chest pain caused by chest wall invasion or skeletal metastasis).
- Chemotherapy is less helpful in non-small-cell type.

2. Small-cell-carcinoma:
- Even small, metastasis occurs early. Surgery is less helpful. Chemotherapy is usually given. Radiotherapy may be added (continuous hyperfractionated accelerated radiotherapy, CHART, in which total dose is given in smaller, but more frequent fractions offer the best survival).

- Usual chemotherapy—intravenous CDV (cyclophosphamide, doxorubicin and vincristine) or CE (cisplatin plus etoposide). Chemotherapy is given every 3 weeks for 3 to 6 cycles.

3. Other treatments: These are usually palliative.
- Laser therapy with fiberoptic bronchoscopy.
- Endobronchial therapy—tracheobronchial stent, cryotherapy, laser, brachytherapy (a radioactive source is placed closed to the tumor).
- RFT (radiofrequency thermal ablation).
- Pleural drainage or pleurodesis (in pleural effusion).
- Drug—steroid to improve appetite, morphine or diamorphine for pain (along with laxatives if constipated). Oral candidiasis should be treated.
- Short courses of palliative radiotherapy are helpful for bone pain, severe cough or hemoptysis.

The RFT is helpful in some malignancy, such as bronchial carcinoma and hepatocellular carcinoma. It is done by placing special needle into the tumor under guidance of CT scan. Electric current from radiofrequency current generator is passed through the needle, which results in generation of heat causing destruction of tumor. RFT is helpful, if the tumor size is < 4 cm. Also, sometimes used in large tumor.

Complications of RFT:
- Bleeding
- Pneumothorax
- Skin burn
- Secondary infection and lung abscess.

TNM classification of lung cancer (it is for non-small-cell carcinoma):
- T—extent of primary tumor
- N—involvement of lymph node
- M—presence of distant metastasis.

Stages for T:
- Tx—Positive cytology only
- T1—< 3 cm in diameter
- T2—> 3 cm in diameter or extends to hilar region or invades visceral pleura or partial atelectasis or extend into main bronchus, but remains 2 cm or more distal to carina
- T3—Involvement of chest wall, diaphragm, pericardium, mediastinum, pleura, total atelectasis, main bronchus < 2 cm distal to carina
- T4—Involvement of heart, great vessels, trachea, esophagus, malignant effusion, vertebral body, carina. Separate tumor nodules.

Stages for N:
- N0—No nodal involvement
- N1—Peribronchial, ipsilateral hilar or intrapulmonary lymph node involvement
- N2—Ipsilateral mediastinal or subcarinal
- N3—Contralateral mediastinal, scalene or supraclavicular.

Stages for M:
- M0—No distant metastasis
- M1—Distant metastasis.

Q. What is the **role of staging?**

A. Staging is done to see the possibility of surgical resection of the carcinoma. TNM staging is done for non small cell cancer only. In early stage, surgery may be curative. In advanced stages, surgery may not be possible. Small cell carcinoma is treated according to whether it is limited or extensive.

Q. What is the **role of surgery** in lung carcinoma?

A. In non-small-cell carcinoma without metastasis, surgery is the treatment of choice. But it has limited role in small cell carcinoma, as more then 90% patient has metastasis at the time of presentation.

Q. What are the **contraindications** of surgery?

A. As follows:

- Distant metastasis (M1)
- Invasion of central mediastinal structures including heart, great vessels, trachea and esophagus (T4)
- Malignant pleural effusion (T4)
- Contralateral mediastinal lymph node involvement (N3)
- $FEV_1 < 0.8$ L
- Poor general condition, severe or unstable cardiac or other medical problem.

Note Remember the following points:

- In a fit individual, surgery is not absolutely contraindicated in case of direct extension of tumor into the chest wall, diaphragm, mediastinal pleura or pericardium or to within 2 cm of the main carina.
- Surgery is rarely appropriate in patients over 65 years as the operative mortality rate exceeds the 5-year survival rate.

Q. What are the **indications of radiotherapy?**

A. As follows:

1. As the main treatment in:
   - Localized tumor where surgery is not possible
   - Along with chemotherapy in small cell carcinoma
   - Before and after surgery in selected patients.
2. As a palliative therapy in:
   - Pain (local or metastasis)
   - Superior vena caval obstruction
   - Pancoast's tumor
   - Obstruction of trachea and main bronchi
   - Recurrent hemoptysis.

Q. What is the role of **chemotherapy**?

A. Small cell carcinoma is usually treated with chemotherapy. Drugs used are cisplatin, etoposide, cyclophosphamide, vinblastine, vindesine, carboplatin. Newer drugs are docetaxel, paclitaxel, irinotecan, vinorelbine, gemcitabine.

Q. What is the **prognosis**?

A. If it is localized and surgical resection is possible, the prognosis is good. Otherwise:

- Non-small-cell carcinoma—50% 2 year survival without spread, 10% with spread
- Small cell carcinoma—median survival is 3 months if untreated, 1 to 1½ year with treatment.

Remember the tumour markers of different tumour

Biochemical markers of tumor—Some biochemical markers in the serum indicates presence of specific carcinoma. Examples are:

- α-fetoprotein—HCC, non seminomatous germ cell tumor of gonads
- β human chorionic gonadotrophin (β-HCG)—choriocarcinoma (100%), hydatidiform mole (97%), ovarian non-seminomatous germ cell tumor (50 to 80%), seminoma, lung cancer
- Prostate specific antigen (PSA)—carcinoma of prostate
- Carcinoembryonic antigen (CEA)—colorectal cancer (commonly with liver metastasis)
- CA-125 (cancer antigen 125)—ovarian cancer (75%), gastrointestinal cancer (10%), lung cancer (5%), breast (5%)
- CA-19-9—pancreatic cancer, may be other gastrointestinal cancer
- CA-15-3—breast cancer
- Osteopontin—mesothelioma and many other cancers
- Thyroglobulin—papillary and follicular thyroid carcinoma
- Calcitonin—medullary carcinoma of thyroid
- Placental alkaline phosphatase (PLAP)—seminoma (40%), ovarian dysgerminoma (50%)
- β_2 microglobullin—myeloma, NHL.

CONSOLIDATION

CHIEF COMPLAINTS

- Fever for … days
- Cough for … days
- Chest pain for … days
- Malaise, generalized bodyache, weakness for ... days.

HISTORY

History of present illness: According to the statement of the patient, he was alright … days back. Since then, he has been suffering from high grade continued fever, highest recorded temperature is 104^0F. The fever is associated with chill and rigor, sometimes with profuse sweating, subsides with paracetamol. The patient also complains of cough for … days, which was initially dry, but for the last few days, the cough is productive with purulent or yellowish sputum. He also complains of left sided chest pain, which is sharp, stabbing in nature, more marked on coughing, and deep inspiration, also on lying on the left side, and there is no radiation of pain. For the last ... days, he is experiencing malaise, generalized bodyache and weakness. There is no history of breathlessness, hemoptysis or contact with TB patient. His bowel and bladder habits are normal. There is no history of traveling, exposure to firm animals or birds.

History of past illness: There is no history of previous lung disease. He is nondiabetic.

Family history

Personal history

Socioeconomic history

Drug history: No history of taking steroid, antibiotic, etc. (immunosuppressive drugs). (Mention according to the patient's statement).

GENERAL EXAMINATION

- Ill looking and toxic
- Pulse: 120/min
- BP: 110/70 mm Hg
- Temperature: 104°F
- Respiratory rate: 30/min
- Herpes labialis in the right angle of mouth (mention if present)
- No anemia, jaundice, cyanosis, clubbing, koilonychia, leukonychia and edema
- No lymphadenopathy or thyromegaly.

SYSTEMIC EXAMINATION

Respiratory System (Supposing in Left Side)

Inspection:

- Movement restricted on the left side.

Palpation:
- Trachea—central in position
- Apex beat—in the left fifth intercostal space medial to the midclavicular line, normal in character
- Vocal fremitus- increased over left side from … to ….
- Chest expansibility—slightly reduced on left side
- Pleural rub is palpable in the left side (mention if any).

Percussion:
- Percussion note is woody dull over … to … spaces on left side of the chest
- Upper border of liver dullness is in right 5th intercostal space in midclavicular line
- Area of cardiac dullness—normal.

Auscultation:
- Breath sound—high pitched bronchial sound over in … spaces in left side
- Vocal resonance is increased and there is whispering pectoriloquy in the same area
- (There are few crepitations and pleural rub on the same area, mention if any).

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 42 years old, Government service holder, normotensive, nondiabetic, nonsmoker, hailing from …, presented with high grade continued fever for … days. The highest recorded temperature is 104°F. The fever is associated with chill and rigor, sometimes with profuse sweating, subsides with paracetamol. The patient also complains of cough for … days, which was initially dry, but for the last few days, the cough is productive with purulent or yellowish sputum. He also complains of left sided chest pain, which is sharp, stabbing in nature, more marked on coughing, and deep inspiration, also on lying on the left side, and there is no radiation of pain. For the last ... days, he is experiencing malaise, generalized bodyache and weakness. There is no history of breathlessness, hemoptysis or contact with TB patient. His bowel and bladder habits are normal. There is no history of traveling, exposure to firm animals or birds. There is no history of previous lung disease. For his illness he took some paracetamol and cough syrup. No history of taking steroid, antibiotic, etc.

On examination – general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is left sided consolidation

Q. What are your **differential diagnoses?**

A. As follows:
- Lung abscess
- Bronchiectasis with secondary infection
- Pleural effusion
- Pulmonary infarction.

Q. **Why not** lung abscess?

A. In case of lung abscess, there will be more profuse foul smelling sputum. Clubbing may be present. Auscultation may show more coarse crepitations. X-ray will show cavity with air fluid level.

Q. Why not **tuberculosis**?

A. With short history, very high temperature and signs of consolidation, tuberculosis is unlikely. In case of TB, there will be low grade continued fever with evening rise, weight loss, anorexia, night sweat, etc.

Q. What is the typical character of sputum in consolidation?

A. The sputum is usually rusty.

Q. Why crepitations in consolidation?

A. Because of resolution.

Q. What investigations should be done in consolidation?

A. As follows:

1. Hb%, TC, DC, ESR:
   - In bacterial pneumonia—polymorphonuclear leukocytosis.
   - In atypical pneumonia—normal or slightly increased leukocytes.
   - In viral pneumonia—leukopenia.
2. X-ray chest: Homogenous opacity with air bronchogram (usually found after 12 to 18 hours). If it is associated with hilar adenopathy, suggestive of *Mycoplasma pneumoniae.*
3. Sputum: Gram staining, C/S (aerobic and anaerobic).
4. Blood C/S (positive in pneumococcal pneumonia).
5. Arterial blood gas analysis.
6. Others (according to etiology):
   - Pneumococcal antigen in serum.
   - Mycoplasma antibody detection (agglutination, CFT), Coomb's test, C/S in special media
   - Antibody against virus, chlamydia, legionella
   - Urinary legionella pneumophila antigen
   - CRP (high).

Note

Chest X-ray may reveal complications, such as pleural effusion and cavitation (found in infection by *Staphylococcus aureus* and pneumococcal serotype 3).

RELATED QUESTIONS AND ANSWERS

Q. What is consolidation?

A. It means pneumonia which is defined as "inflammation in the lung characterized by accumulation of secretion and inflammatory cells in alveoli".

Q. What are the types of pneumonia?

A. As follows:

1. Anatomically 2 types:
   - Lobar: Commonly involves one or more lobe.
   - Lobular (bronchopneumonia): It is characterized by nonpatchy alveolar opacity with bronchial and bronchiolar inflammation. Commonly, involves both lower lobes.

2. Clinically 4 types:
   - Community acquired pneumonia (CAP)
   - Nosocomial pneumonia (hospital acquired)
   - Pneumonia in immunocompromised
   - Suppurative and aspiration pneumonia.

Q. What are the causes of community acquired pneumonia (CAP)?

A. It is caused by:

- Common organism: Streptococcus pneumoniae (50%), *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila.*
- Others: *Staphylococcus aureus*, *Haemophilus influenzae*, *Chlamydia psittaci*, *Coxiella burnetii* (Q fever), *Klebsiella*, *Actinomyces* israelii and viral (influenza, parainfluenza, measles, respiratory syncytial virus in infancy and varicella) infections.

Note Remember the following points:

- CAP usually spread by droplet infection and most cases occur in previously healthy individual
- Physical signs of consolidation develops in 2 days, disappears after 2 weeks
- Radiological signs develop 12 to 18 hours after the onset and usually disappear within 4 weeks.

Q. What are the **precipitating factors** of pneumonia?

A. As follows:

- *Streptococcus pneumonia* often follows viral infection with influenza or parainfluenza virus
- Hospitalized ill patient
- Smoking
- Alcohol excess
- Bronchiectasis (e.g. in cystic fibrosis)
- Bronchial obstruction
- Immunosuppression
- IV drug abuser
- Inhalation from esophageal obstruction.

Q. What are the pathological stages of CAP?

A. Four stages:

- Stage of congestion—persists for 1 to 2 days
- Stage of red hepatization (red and solid like liver)—persists for 2 to 4 days
- Stage of grey hepatization—persists for 4 to 8 days
- Stage of resolution—8 to 9 days or more.

Q. What are the **presentations** of lobar pneumonia?

A. The patient may present with:

- Fever, may be with chill and rigor
- Cough, initially short, painful and dry. Later on, expectoration (during resolution). Rusty sputum (due to *Streptococcus pneumoniae*)
- May be hemoptysis
- Chest pain, pleuritic (may radiate to shoulder or abdomen)
- Other features—dyspnea, anorexia, nausea and vomiting.

Q. What are the **complications** of pneumonia?

A. As follows:

- Pulmonary—lung abscess, pleurisy, pleural effusion, empyema thoracis, pneumothorax by *Staphylococcus aureus*, fibrosis of lung, collapse, adult respiratory distress syndrome (ARDS), delayed or slow resolution
- Cardiovascular—pericarditis, myocarditis, endocarditis, arrhythmia, thromboembolic disease and peripheral circulatory failure
- Neurological—meningism, meningoencephalitis
- Musculoskeletal—septic arthritis

- GIT—meteorism (gaseous distension of stomach, intestine or abdomen).
- Others—septicemia, renal failure, hepatitis, ectopic abscess formation by *Staphylococcus aureus*.

Q. How to **differentiate** between bacterial and viral pneumonia?

A. As follows:

Topic	Bacterial pneumonia	Viral pneumonia
1. Onset	Abrupt, high fever with chill and rigor	Less abrupt, history of upper respiratory tract infection and low-grade fever, headache and malaise
2. Cough	Initially dry, later rusty sputum or purulent	Usually dry (extrathoracic complains are more)
3. Pleuritic chest pain	Common.	Less common (respiratory complaints are less common, constitutional symptoms predominate)
4. Physical signs of consolidation	Well marked	Minimal
5. Blood count	Leukocytosis	Normal or leukopenia.
6. Chest X-ray	Lobar or segmental homogeneous opacity with air bronchogram	Mottling or reticular pattern or patchy opacity or streaky
7. C/S	Organism found	No organism

Q. What are the causes of **slow or delayed resolution** of pneumonia?

A. Delayed resolution means when the physical signs persist for more than 2 weeks and radiological features persist for more than 4 weeks after antibiotic therapy. Causes are:

- Incorrect microbiological diagnosis
- Fungal, tubercular or atypical pneumonia
- Improper antibiotic or insufficient dose
- Bronchial obstruction (bronchial carcinoma, adenoma, foreign body)
- Empyema or atelectasis
- Immunocompromised patient (HIV, DM, lymphoma, leukemia, multiple myeloma).

Note Remember the following points:

- Physical signs of consolidation may appear within 2 days, and disappear within 2 weeks with proper treatment
- Radiological opacity appears within 12 to 18 hours, and disappears within 4 weeks with proper treatment
- If radiological opacity persists after 8 weeks (with treatment), it is called non-resolution

Q. What are the causes of **recurrent pneumonia** (3 or more separate attack)?

A. As follows:

- Bronchial obstruction (bronchial carcinoma, adenoma, foreign body)
- Lung disease (bronchiectasis, lung abscess, cystic fibrosis, sequestrate segment of lung—commonly left lower lobe)

- Aspiration (achalasia cardia, scleroderma, pharyngeal pouch)
- Immunocompromised patient (HIV, DM, lymphoma, leukemia, multiple myeloma).

Q. What are the **criteria** of assessment of severity of CAP?

A. CURB-65 criteria may be used for the assessment of severity of CAP. 1 point is scored for each of the following features:

- **C**onfusion (mini mental score 8 or less or new disorientation in person, place or time)
- **U**rea > 7 mmol/L or > 20 mg/dL
- **R**espiratory rate > 30 /min
- **B**lood pressure (systolic BP < 90 mm Hg and diastolic BP < 60 mm Hg)
- Age > **65** years.

This score is used for management:

- Score 0 or 1—home treatment
- Score 2—hospitalization
- Score 3 or more—manage in hospital, may require ICU.

Other markers of severity of pneumonia

- Chest X-ray—more than one lobe involved
- PaO_2 < 8 κPa
- Low albumin (<35 g/L)
- White cell count (<4,000/cmm or >20,000/cmm)
- Blood culture positive.

Q. What are the **indications** for referral for ITU?

A. As follows:

- CURB score 4 to 5
- Persistent hypoxia despite high concentration of oxygen (PO_2 < 8 κPa or 60 mm Hg)
- Progressive hypercapnia
- Severe acidosis
- Shock
- Depressed consciousness.

Q. What is **nosocomial pneumonia?** What are the **causes** and **predisposing factors**?

A. New episode of pneumonia occurring at least 2 days after admission in the hospital is called nosocomial pneumonia.

Causes are: If it occurs within 4 to 5 days of admission (early onset), organisms are similar to CAP. However, if it occurs later (late onset), common organisms are:

- Gram-negative enterobacteriaceae *(Escherichia coli, Klebsiella and Pseudomonas aeruginosa)* are common
- *Staphylococcus aureus* including methicillin-resistant *Staphylococcus aureus* (MRSA)
- Anaerobic organism.

Predisposing factors:

- Elderly patient
- Bed bound, unconscious (e.g. CVA)
- Postoperative case (thoracic or abdominal surgery)
- Malignancy
- Diabetes mellitus
- Use of steroid, cytotoxic drugs, antibiotics
- Prolonged anesthesia, intubation, tracheostomy, IV canula

- Achalasia of cardia, dysphagia due to any cause, vomiting
- Bulbar or vocal cord palsy
- Nasogastric intubation
- Abdominal sepsis, infected emboli.

Q. How to **diagnose** nosocomial pneumonia?

A. After admission in the hospital, associated with predisposing factors, if the patient develops purulent sputum, fever associated with radiological infiltrate, leukocytosis or leukopenia unexplained increase in oxygen requirement.

Q. How to treat **nosocomial pneumonia?**

A. Empirical antibiotic therapy should be started which should cover Gram-negative organisms:

- A third generation cephalosporin (e.g. cefotaxime) with an aminoglycoside (gentamicin)
- Meropenem or
- A monocyclic beta lactam (e.g. aztreonam) and flucloxacillin
- MRSA is treated with IV vancomycin. When possible, oral therapy may be considered with doxycycline, rifampicin or linezolid
- If pseudomonas infection is suspected: IV ciprofloxacin or ceftazidime should be given.

Note

Aspiration pneumonia is also common in hospital and involves multiple organism with anaerobe. Treatment—IV co-amoxiclav or cefuroxime plus metronidazole.

Physiotherapy and oxygen therapy, fluid support and monitoring are also essential.

Q. What is **bronchopneumonia**?

A. It is defined as wide spread diffuse patchy alveolar opacity associated with bronchial and bronchiolar inflammation, often affecting both lower lobes. In children, it occurs as a complication of measles or whooping cough and in elderly, a complication following bronchitis or influenza.

Q. What is **typical pneumonia?**

A. Typical pneumonia is characterized by high temperature with cough, pleuritic chest pain, features of consolidation, caused by *Streptococcus pneumoniae*, *Staphylococcus aureus*, etc. Respiratory symptoms are more with constitutional symptoms.

Q. What is **atypical pneumonia?**

A. When pneumonia is caused by mycoplasma, legionella, coxiella, chlamydia. In these cases, constitutional symptoms are more than respiratory symptoms. Features are:

- Gradual onset
- Dry cough
- Low grade fever
- Constitutional symptoms are more than respiratory symptoms (headache, myalgia, fatigue, nausea, vomiting)
- Less physical finding in the chest.

Q. How to **diagnose and treat** *Mycoplasma pneumoniae?*

A. It is common in children and young adult and is usually associated with headache, malaise and severe cough. Physical signs are less marked. Epidemics occur in cycle every 3 to 4 years.

Investigations**:**

- WBC (normal)
- Chest X-ray (commonly lower lobe involvement), may show bilateral patchy consolidation
- Cold agglutinin (positive in 50% cases)
- Rising antibody titer for *Mycoplasma pneumoniae*
- Others (CFT and hemagglutination test).

Extrapulmonary complications of *Mycoplasma pneumonia:*

- Maculopapular skin rash, erythema multiforme and Stevens Johnson syndrome
- Myocarditis and pericarditis
- Hemolytic anemia (Coombs test may be positive) and thrombocytopenia
- Meningoencephalitis, GBS and other neurological abnormalities
- Myalgia and arthralgia
- Gastrointestinal symptoms like vomiting, diarrhea.

Treatment:

- Clarithromycin 500 mg twice daily orally or IV or
  Erythromycin 500 mg 6 hourly orally or IV for 7 to 10 days
- **Or,** Doxycycline 100 mg twice daily
- Rifampicin 600 mg 12 hourly.

Note

The term atypical pneumonia is abandoned

Q. How to **diagnose and treat** *Legionella pneumophila?*

A. Three patterns of Legionnaires' disease may occur:

- Outbreak of infection is usually associated with contaminated water supply or cooling system, or from stagnant water in cistern or shower head.
- Sporadic case, where source is unknown. It is usually common in middle aged and elderly, more in smokers.
- Outbreaks may occur in immunocompromised patients as for example those on corticosteroid therapy. Diabetes and CKD also increase risk.

Features are: Initially viral-like illness with high fever, chill and rigor, malaise, myalgia and headache. Dry cough, which is later productive and purulent. There may be nausea, vomiting, diarrhea and pain abdomen. Mental confusion and other neurological signs, even coma may be present. Occasionally, renal failure and hematuria may be seen.

Investigations:

- WBC—lymphopenia without marked leukocytosis.
- Chest X-ray—usually shows lobar and then multilobar shadowing. A small pleural effusion may be present. Cavitation is rare
- Hyponatremia
- Hypoalbuminemia
- High serum aminotransferases, creatine phosphokinase
- Direct immunofluorescent for Legionella in pleural fluid, sputum or bronchial washings. Culture on special media can be done, but takes 3 weeks
- Legionella serology—4 fold rise is highly suggestive
- Urine for antigen (highly specific)
- Urine R/E shows hematuria.

Treatment:
- Clarithromycin 500 mg twice daily orally or IV or
  Erythromycin 500 mg 6 hourly orally or IV for 7 to 10 days
- Rifampicin 600 mg 12 hourly.

Prognosis: 10% mortality (may be up to 30% in elderly).

Q. How to **treat** pneumonia?

A. Sputum should be sent for C/S and antibiotic should be started. The treatment involves:

1. General treatment—rest, O_2 therapy, adequate hydration and chest physiotherapy

2. Antibiotic (empirically with suspicion of cause).

Community acquired pneumonia (CAP):

1. Mild CAP:
- Amoxicillin 500 mg 8 hourly orally or erythromycin 500 mg 6 hourly or clarithromicin 500 mg twice daily or azithromycin 500 mg daily
- If *Staphylococcus aureus* is suspected—clarithromycin 500 mg twice daily orally or IV, **plus** flucloxacillin 1 to 2 g 6 hourly IV
- If *Klebsiella* is suspected—ciprofloxacin 200 mg IV 12 hourly, **plus** gentamycin 60 to 80 mg IV 8 hourly (see serum creatinine level) or gentamicin plus ceftazidime 1 g IV 8 hourly

Duration of treatment: 7 to 10 days (up to 14 days):
- If *Mycoplasma, Legionella* or atypical organism is suspected—clarithromycin 500 mg twice daily orally or erythromycin 500 mg 6 hourly orally, or tetracycline or doxycycline may be used.

Duration of treatment: 2 to 3 weeks.

2. Severe CAP:
- Clarithromycin 500 mg twice daily IV or erythromycin 500 mg 6 hourly IV
- **Plus** add one of the following:
  i. Co-amoxiclav 1 to 2 g 8 hourly IV
  ii. Cefuroxime 1.5 g 8 hourly IV
  iii. Ceftriaxone 1 to 2 g IV daily
  iv. Amoxicillin 1 g 6 hourly IV.
  v. If *Staphylococcus aureus* is suspected—flucloxacillin 2 g 6 hourly IV or sodium fusidate is added.

Q. What are the criteria for **discharge** of a patient with pneumonia from hospital?

A. To discharge, the patient should be clinically stable with no more than one of the following clinical signs:
- Temperature > 37.8 ºC
- Heart rate > 100/min
- Respiratory rate > 24/min
- Systolic BP < 90 mm Hg
- SaO_2 < 90%
- Inability to maintain oral intake
- Abnormal mental status.

PNEUMOTHORAX

CHIEF COMPLAINTS

- Breathlessness for … days
- Right sided chest pain for … days
- Cough for … days.

HISTORY

History of present illness: According to the statement of the patient, he was alright … days back. Since then, he suddenly felt severe breathlessness associated with pain in right side of his chest. Breathlessness is present in rest, more marked on lying on right side and also on lying flat. It is non-progressive, not associated with wheeze and does not relieve by taking rest or drugs. He also complains of right sided chest pain, which is sharp and stabbing in nature, aggravated by deep breathing, coughing, with movement and lying on right side but no radiation. The patient also complains of cough with slight mucoid expectoration but no hemoptysis. There is no history of trauma or fever.

History of past illness: There is no history suggestive of COPD, or chronic bronchitis or bronchial asthma. There is no previous attack of such illness.

Family history: Nothing contributory.

Socioeconomic history: He is a laborer, living in a slum area with poor sanitary facilities.

Personal history: He smokes 30 to 40 sticks/day for 20 years, but nonalcoholic.

GENERAL EXAMINATION

- The patient appears anxious and slightly dyspneic
- Decubitus: patient prefers to lie on left lateral position
- He is mildly anemic
- No jaundice, cyanosis, edema, clubbing, koilonychia or leukonychia
- No lymphadenopathy or thyromegaly
- Respiratory rate: 34/min
- BP: 110/80 mm Hg
- Pulse: 108/min.

SYSTEMIC EXAMINATION

Respiratory System (Supposing Right Side)

Inspection:

- Restricted movement on right side of the chest
- Intercostal spaces appear full.

Palpation:

- Trachea—deviated to the left
- Apex beat—in left 6th intercostal space in anterior axillary line (shifted to left), normal in character
- Vocal fremitus—reduced in right side but normal on the left side
- Chest expansion—reduced on the right side of the chest.

Percussion:
- Hyper-resonance in right side (tell where), but normal on the left side
- Upper border of the liver dullness—in the right 6th intercostal space in the midclavicular line.

Auscultation:
- Breath sound—diminished (or absent) on the right side of the chest (tell up to which space), but vesicular on the left side.
- Vocal resonance—diminished (or absent) on the right side of the chest (tell up to which space), but normal on the left side.

Examination of other systems reveals nothing abnormal.

SALIENT FEATURES

Mr …, 38 years, laborer, normotensive, nondiabetic, heavy smoker, hailing from …, presented with sudden severe breathlessness associated with right sided chest pain for … days. Breathlessness is present in rest, more marked on lying on right side and also on lying flat. It is non-progressive, not associated with wheeze and does not relieve by taking rest or drugs. He also complains of right sided chest pain, which is sharp and stabbing in nature, aggravated by deep breathing, coughing, with movement and lying on right side but no radiation. The patient also complains of cough with slight mucoid expectoration but no hemoptysis. There is no history of trauma or fever. There is no history suggestive of COPD, or chronic bronchitis or bronchial asthma. There is no such illness in the past. He smokes 30 to 40 sticks a day for last 20 years. There is no family history of such illness.

On examination, general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is right sided pneumothorax

Q. What are your **differential diagnoses?**

A. As follows:
- Big pulmonary cavity
- Giant bullae.

Q. Mention **one single** investigation for your diagnosis.

A. X-ray chest P/A view.

Q. What **investigations** do you suggest?

A. As follows:
- Complete blood count and ESR
- Chest X-ray P/A view
- Sometimes, CT scan of chest.

RELATED QUESTIONS AND ANSWERS

Q. What is **pneumothorax?**

A. Pneumothorax means presence of air in the pleural cavity.

Q. What is the **usual presentation** of pneumothorax?

A. The patient usually presents with sudden onset of unilateral pleuritic chest pain and breathlessness.

Q. What are the **definitive signs** of pneumothorax?

A. Hyper-resonance on percussion and diminished or absent breath sound.

Q. What are the **types** of pneumothorax?

A. As follows:

1. Spontaneous: It may be primary and secondary

2. Traumatic.

Q. What are the **causes** of pneumothorax?

A. As follows:

1. Spontaneous:

a. Primary: Without underlying lung disease. It is due to:
   - Rupture of apical subpleural bleb due to congenital defect in connective tissue of alveolar walls. Common in young, 15 to 30 years of age. M:F ratio is 4:1. The patient is tall, lean and thin, there is 25% chance of recurrence.
   - Rupture of emphysematous bullae or pulmonary end of pleural adhesion.

b. Secondary: Occurs in pre-existing lung disease. Causes are:
   - Commonly COPD and tuberculosis.
   - Others—lung abscess, acute severe asthma, bronchial carcinoma, pulmonary infarction, all forms of fibrotic and cystic lung disease, Marfan's syndrome, Ehlers-Danlos syndrome and eosinophilic granuloma.

2. Traumatic:

a. Iatrogenic—during aspiration of pleural fluid, thoracic surgery, lung biopsy or pleural biopsy, positive pressure ventilation, thoracocentesis and subclavian vein catheterization.

b. Chest wall injury.

Note Remember the following points:

- In young patient, common cause is rupture of subpleural bleb
- In patient > 40 years of age, common cause is chronic bronchitis with emphysema

Q. What are the **types** of spontaneous pneumothorax?

A. Three types (anatomical):

1. Closed—communication between the lung and pleural space is sealed off. Intrapleural pressure is less than atmospheric pressure. Trapped air is slowly reabsorbed, lung reexpands in 2 to 4 weeks. Closed pneumothorax may be mild, moderate and large.
2. Open—communication between the lung and pleural space persists (bronchopleural fistula). Intrapleural pressure and atmospheric pressure are equal throughout the respiratory cycle, which prevents re-expansion of the collapsed lung. Hydropneumothorax develops. Infection is common and empyema develops. Physical examination shows features of hydropneumothorax. Causes are:
   - Rupture of emphysematous bullae
   - Small pleural bleb
   - Tuberculous cavity
   - Lung abscess bursting into pleural cavity.
3. Valvular—There is a communication between the pleura and the lung which acts as a one-way valve allowing air to enter into the pleural space during inspiration, but does not let air escape on expiration. Intrapleural pressure becomes greater than the atmospheric pressure. It results in compression of the lung, shifting of mediastinum to the opposite side, compression of heart and the opposite lung also. It reduces the venous return by compressing the SVC. There is rapidly progressing breathlessness, cyanosis, shock, etc. It is a medical emergency, death may occur within minutes.

Note Remember the following:

Normal intrapleural pressure is negative (subatmospheric), usually – 2.5 to – 6.0 mm Hg.

Q. How would you **grade** pneumothorax?

A. According to British Thoracic Society:

- Mild—small rim of air around the lung, <20% of the radiographic volume
- Moderate—lung collapse, >20 to 50% of the radiographic volume
- Large—lung collapse, >50% of the radiographic volume
- Tension—pneumothorax with cardiorespiratory distress, features of shock.

Q. What are the **causes of recurrent pneumothorax** (more than twice)? How to **treat**?

A. Causes are:

- Apical subpleural bleb or cyst (congenital)
- Emphysematous bullae
- Cystic fibrosis
- Others—Marfan's syndrome, catamenial pneumothorax, Ehlers-Danlos syndrome, α_1- antitrypsin deficiency and histiocytosis X, honeycomb lung.

Treatment:

1. Chemical pleurodesis. Done by injecting tetracycline (500 mg), kaolin or talc into the pleural cavity through intercostal tube.
2. Surgical pleurodesis. Done by parietal pleurectomy or pleural abrasion during thoracotomy or thoracoscopy. Indications are:
   - All patients after a second pneumothorax
   - Considered after first episode of secondary pneumothorax, if there is low respiratory reserve
   - Patient who plan to continue activity, where pneumothorax would be particularly dangerous (e.g. flying or diving) should undergo definitive treatment after first episode of primary spontaneous pneumothorax.

Note Remember the following:

Pleurodesis is avoided in patient with cystic fibrosis, as lung transplantation may be required and pleurodesis may make this condition technically not feasible.

Q. What are the indications of **surgery (open thoracotomy)?**

A. As follows:

- Failure of the lung to re-expand after 5 days of tube thoracotomy
- Recurrence (usually on third recurrence)
- Bilateral pneumothorax.

Q. What is **coin test?**

A. In this test, one coin is placed on the front or back of the chest and struck with edge of another coin. At the same time auscultated on the opposite side of the chest at the same level. There will be a metallic, bell-like sound if pneumothorax is present.

Q. What is **catamenial pneumothorax?**

A. If pneumothorax develops at the time of menstruation, it is called catamenial pneumothorax. It is usually on the right side, occurs within 48 hours of onset of menstruation, common in 25 to 30 year old female and is due to intrapleural endometriosis.

It is treated by hormone therapy to suppress ovulation (by progesterone or androgen therapy) or simply by oral contraceptive pills. Sometimes, surgical exploration and pleurodesis may be needed.

Q. What is **tension pneumothorax?** What are the **causes?** How to **treat?**

A. It is a valvular-type of pneumothorax, in which there is a communication between lung and pleural cavity with one-way valve, which allows air to enter during inspiration and prevents to leave during expiration. It causes shifting of mediastinum to the opposite side and compresses the heart and opposite lung.

Features of tension pneumothorax:

- Severe chest pain (pain is worse with cough and relieve on sitting position)
- Severe and progressively increasing dyspnea
- Cough
- Tachypnea, tachycardia, pulsus paradoxus
- Features of shock (hypotension, central cyanosis and tachycardia)
- Raised JVP, engorged neck vein due to compression of the heart
- Shifting of mediastinum to the opposite side.

Note

Cardinal features are progressively increasing dyspnea and features of shock.

Causes of tension pneumothorax:

- Traumatic
- Mechanical ventilation at high pressure
- Rarely, spontaneous pneumothorax.

Treatment:

- Immediate insertion of wide bore needle in second intercostal space in midclavicular line, with the patient is sitting position.
- Intrathoracic tube is inserted in fourth, fifth or sixth intercostal space in midaxillary line, and the tip of the tube should be advanced in apical direction. It is connected to a underwater seal or one-way Heimlich valve.
- The patient should be kept propped up with oxygen inhalation.
- Morphine 5 to 10 mg subcutaneously.
- If bubbling ceases, repeat chest X-ray. If the lung re-expands, tube may be removed after 24 hours. Tube should be removed during expiration or Valsalva maneuver (the tube need not be clamped before removing).
- If no response or continued bubbling for 5 to 7 days, surgical treatment may be necessary.

Q. How do you know that the **water seal drainage** is working properly or not?

A. As follows:

- Bubbling of air in water
- During expiration or coughing, more bubbling occurs
- During inspiration, water column ascends within the tube, which remains under water.

Q. What **advice** is given to the patient with **water seal drainage?**

A. Never raise the bottle above the chest wall. The bottle must be kept below the level of thorax. The patient is also advised to inflate air pillows or balloons which will help in the expansion of collapsed lung.

Q. What are the **indications** of chest tube or IT tube drainage?

A. As follows:

- Tension pneumothorax
- Large second spontaneous pneumothorax if > 50 years
- Malignant pleural effusion
- Empyema thoracis or complicated parapneumonic effusion
- Hydropneumothorax
- Traumatic hemopneumothorax
- Postoperatively as for example thoracotomy, esophagectomy, cardiothoracic surgery.

Q. How to **follow-up** a patient after chest tube insertion?

A. As follows:

- Bubbling—whether it disappears or persistent (indicates leaking)
- Blockage of the tube by clot or kinking
- Malposition
- Retrograde flow back into the chest.

Q. How to **treat** pneumothorax?

A. Depends on whether it is primary or secondary, open, closed or tension or presence of symptoms.

1. In primary small pneumothorax:
   - Spontaneous resolution occurs. Follow-up at 2-week interval (repeat chest X-ray)
   - Normal activity
   - Avoid strenuous exercise
2. In primary moderate to large with breathlessness: Percutaneous needle aspiration of air (2 to 5 litre. Stop, if resistance to suction is felt or patient coughs).
3. In secondary pneumothorax: Patient with COPD, even small pneumothorax can cause respiratory failure. Hence, water seal drainage should be given.
4. Open pneumothorax: Surgery (as is due to bronchopleural fistula).
5. Tension pneumothorax (described as above).

Advice to the patient:

- Must stop smoking
- Avoid air travel for 6 weeks after normal chest X-ray
- Diving should be permanently avoided.

Q. If you are working in a **remote place** and a patient presents with tension pneumothorax, what measures should you take?

A. Immediately I shall insert a wide bore needle (may be cannula/venflon) in the second intercostal space in midclavicular line. This will allow the trapped air to escape (producing an audible hiss). Then I shall send the patient to the nearest hospital (do not remove the cannula, tape it securely).

Q. How long the lung takes to **re-expand?**

A. Air is absorbed at the rate of 1.25% of the total radiographic volume/day. So, if there is 50% lung collapse, it will take 40 days to expand.

Q. What are the possible causes of **failure of re-expansion** of lung?

A. As follows:

- Water seal drainage is not working properly or may be blocked.
- Presence of bronchopleural fistula.
- A major bronchus may be obstructed.
- Lung is completely fibrosed with permanent damage.

Q. What is **hydropneumothorax?** What are the **causes?** How to **manage?**

A. When there is accumulation of fluid and air in pleural cavity, it is called hydropneumothorax.

Its **causes** are:

- Iatrogenic (during aspiration of pleural fluid)
- Pulmonary tuberculosis
- Bronchopleural fistula
- Trauma (penetrating chest injury and thoracic surgery)
- Rupture of lung abscess
- Esophageal rupture
- Erosion of bronchial carcinoma.

Management**:** Water seal drainage and treatment of primary cause.

Q. What is the **bedside test** of hydropneumothorax?

A. Succusion splash.

Q. What are the **signs** of hydropneumothorax?

A. In lower part, signs of pleural effusion and in upper part, signs of pneumothorax.

COLLAPSE OF THE LUNG

CHIEF COMPLAINTS

- Frequent cough for … months
- Breathlessness for … days
- Weight loss, malaise, anorexia for … days.

HISTORY

History of present illness: According to the statement of the patient, he was alright … months back. Since then, he has been suffering from severe dry cough, which is present throughout the day and night. Cough is worse on lying position, also occasionally it is aggravated on exposure to cold and dust. The patient also complains of breathlessness, which is usually on moderate to severe exertion, but there is no history of orthopnea or paroxysmal nocturnal dyspnea. For last … days, he also complains of loss of appetite and marked weight loss. There is no history of fever or haemoptysis or contact with TB patients.

History of past illness: He was suffering from some lung disease, the nature of which he could not mention.

Family history: Nothing significant.

Personal history: He smokes about 20 sticks/day for 20 years, but nonalcoholic.

Socioeconomic history: He works in a pillow shop where he sorts cotton and makes pillows and blankets.

Drug history: Nothing significant.

GENERAL EXAMINATION

- The patient is ill-looking and emaciated, dyspneic
- Mildly anemic
- Clubbing: There are generalized clubbing involving toes and fingers, but no hypertrophic osteoarthropathy
- No jaundice, cyanosis koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- Pulse:100/min
- BP: 100/60 mm Hg
- Respiratory rate: 28/min.

SYSTEMIC EXAMINATION

Respiratory System (Supposing Right of Chest)

Inspection:

- Restricted movement on the right side
- Flattening on the upper part and crowding of ribs
- Drooping of the right shoulder.

Palpation:
- Trachea: Shifted to the right
- Apex beat: Shifted to the right (tell where)
- Vocal fremitus: Reduced (or increased) in the right side (tell up to where).

Percussion:
- Dullness in the right upper part of the chest (tell up to where)
- Upper border of liver dullness is in the right 4th intercostal space in the midclavicular line.

Auscultation:
- Breath sound: Bronchial (or reduced) on right side of the chest (tell up to where).
- Added sound: Some coarse crepitations are found on the right side of the chest (tell which spaces).
- Vocal resonance: Increased in right upper chest (or decreased), there is whispering pectoriloquy (present, if bronchial sound is present).

Note Signs of collapse depend on patency of the bronchus:
- If bronchus is completely obstructed (usually central collapse), all the signs will be collapsed (absent or reduced). Breathsound is diminished or absent. Vocal resonance is diminished or absent.
- If bronchus is patent (peripheral collapse), there is bronchial sound and increased vocal resonance.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 45 years, cotton sorter, normotensive, nondiabetic, smoker, hailing from …, presented with severe dry cough for … months. The cough is present throughout the day and night. It is worse on lying position, also occasionally it is aggravated on exposure to cold and dust. The patient also complains of breathlessness, which is usually on moderate to severe exertion, but there is no history of orthopnea or paroxysmal nocturnal dyspnea. For last … days, he also complains of loss of appetite and marked weight loss. There is no history of fever or hemoptysis or contact with TB patients. He was suffering from some lung disease, the nature of which he could not mention. He smokes about 20 sticks/day for 20 years.

On examination, general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is right sided lung collapse.

Q. What are your **differential diagnoses?**

A. Fibrosis of the lung.

Q. Why not **fibrosis?**

A. It may be fibrosis, but there are certain differentiating points. As fibrosis is a chronic process, the following findings are highly suggestive of fibrosis:
- Flattening of chest on the affected side
- Crowding of the ribs
- Drooping of the shoulder

These findings may be present in collapse as well, if it is prolonged. All other signs of collapse are same as in fibrosis, but with less degree.

Q. How to **confirm** your diagnosis?

A. X-ray chest PA view**:**

- In collapse: There is homogenous opacity with clear lung margin. Evidence of bronchial obstruction (mass lesion) may be seen, diaphragm may be elevated.
- In fibrosis: Nonhomogenous opacity, rib crowding and ring shadow due to dilatation of bronchi within fibrosis may be seen.

Q. Why not this is a case of **consolidation?**

A. In consolidation, trachea and apex beat will not be shifted and percussion is woody dull.

Q. Why not this is a case of **pleural effusion?**

A. In pleural effusion, trachea and apex beat are shifted to the opposite side.

Q. Why not this is a case of **thickened pleura?**

A. In thickened pleura, there is no shifting of the trachea and the apex beat.

Q. What **investigations** should be done in collapse of lung?

A. As follows:

- CBC
- Chest X-ray, PA view (homogenous opacity, heart and lung shifted to the affected side), and lateral view, if needed
- CT scan of chest
- Bronchoscopy (to see any obstruction, removal of foreign body, aspiration of any material, biopsy).

RELATED QUESTIONS AND ANSWERS

Q. What are the **types** of collapse?

A. As follows:

I. Etiologically:

1. Compression collapse (passive)—due to pleural effusion, pneumothorax and hydropneumothorax. Trachea and apex beat are shifted to the opposite side.
2. Absorption collapse (active)—caused by bronchial obstruction due to any cause. Air is absorbed distal to the obstruction and affected part is collapsed. Causes are:
   - Neoplasm (bronchial carcinoma, adenoma)
   - Foreign body (inert object and artificial teeth)
   - Mucous plug (due to bronchial asthma, cystic fibrosis, postoperative)
   - Aspergilloma
   - Pressure on bronchus from outside (enlarged lymph node, aortic aneurysm, pericardial effusion causing collapse of left lung and enlarged left atrium in mitral stenosis)
   - Rarely, congenital collapse due to absence of surfactant.

II. Anatomically:

1. Central—mass lesion (shows more signs and symptoms).
2. Peripheral—usually small collapse (shows less signs and symptoms).

Causes of collapse according to age:

- Neonate—congenital due to low or absent surfactant, aspiration of meconium.
- Children—foreign body.
- Young—bronchial adenoma and foreign body.
- Elderly—bronchial carcinoma and foreign body (artificial tooth).

Q. How can you **differentiate** central and peripheral collapse clinically?

A. As follows:

- In central collapse—bronchus is completely obstructed. So, breath sound is diminished or absent. Vocal resonance is diminished or absent.
- In peripheral collapse—bronchus is patent. So, breath sound is bronchial and vocal resonance is increased.

Note The most Common cause of collapse:

- Central – brochial carcinoma or adenoma, enlarged lymph node or foreign body.
- Peripheral – mucus plugging, bronchial cast.

Q. What is **middle lobe syndrome?**

A. Middle lobe syndrome is the recurrent or persistent atelectasis of right middle lobe.

The right middle lobe originates at an acute angle and is completely surrounded by lymph nodes. It is frequently obstructed by the enlarged lymph nodes due to malignancy or TB causing collapse of the lobe. There may be bronchiectatic changes. Foreign body may also be responsible.

Diagnosis:

- CT scan or MRI may be done
- Bronchoscopy is also helpful.

SUPERIOR VENA CAVA (SVC) OBSTRUCTION

CHIEF COMPLAINTS

- Cough with mild expectoration for … months
- Loss of appetite and weight loss for … months
- Gradual swelling of the face and arms for … days
- Headache for ... days.

HISTORY

History of present illness: According to the statement of the patient, he was alright … months back. Since then, he has been suffering from frequent cough which is present throughout the day and night. The cough is usually dry, sometimes associated with scanty mucoid expectoration. He also noticed small amount of blood with sputum several times. The patient also complains of loss of appetite and substantial weight loss for the same duration. There is no history of fever, chest pain or contact with TB patients. For the last … days, he noticed gradual swelling of the face and arms along with shortness of breath, which is more marked on exertion. The patient also complains of headache, mostly the vertex, which is aggravated by cough and movement of the head for the same duration. He denies any change of voice, back pain, yellow coloration of urine and sclera. His bowel and bladder habits are normal.

History of past illness: Nothing significant.

Family history: Nothing significant.

Personal history: He smokes about 30 sticks/day for 25 years, but nonalcoholic.

Socioeconomic history: Mention according to the patient's statement.

Drug history: Nothing significant.

GENERAL EXAMINATION

- The patient is dyspneic and emaciated.
- Face is edematous, red, plethoric and cyanosed.
- Eyes are red with congested conjunctiva (blood shot eyes), conjunctival edema (chemosis) and periorbital edema.
- Neck is swollen with engorged, non-pulsatile neck veins.
- Visible tortuous veins in chest wall and abdomen, flow is downwards.
- Upper limbs are edematous with prominent engorged veins.
- Generalized clubbing involving toes and fingers, but no hypertrophic osteoarthropathy.
- No anemia, jaundice, cyanosis, koilonychia, leukonychia or pedal edema.
- No lymphadenopathy or thyromegaly.
- Pulse: 110/min.
- BP: 90/60 mm Hg.
- Respiratory rate: 28/min.

SYSTEMIC EXAMINATION

Respiratory System

(Supposing right sided)

Inspection:

- Shape—normal
- Movement is restricted on right upper chest
- Dilated veins visible on chest and back, flow is above downward.

Palpation:

- Trachea is central in position
- Apex beat—on left 5th intercostal space, 9 cm from midline, normal in character
- Vocal fremitus is reduced in right upper chest.

Percussion:

- Percussion note is dull in right upper chest
- Upper border of liver dullness is in the right 5th intercostal space in the midclavicular line
- Cardiac dullness is normal.

Auscultation:

- Breath sound is reduced on right upper chest
- Vocal resonance is reduced
- Few crepitations (may be present, mention where).

Fundoscopy shows dilated vessels, hemorrhage, exudate, rarely papilledema.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr ..., 65 years old, smoker, normotensive, nondiabetic, hailing from ..., presented with frequent cough for ... months, which is present throughout the day and night. The cough is usually dry, sometimes associated with scanty mucoid expectoration. He also noticed small amount of blood with sputum several times. The patient also complains of loss of appetite and substantial weight loss for the same duration. There is no history of fever, chest pain or contact with TB patients. For the last … days, he noticed gradual swelling of the face and arms along with shortness of breath, which is more marked on exertion. The patient also complains of headache, mostly the vertex, which is aggravated by cough and movement of the head for the same duration. He denies any change of voice, back pain, yellow coloration of urine and sclera. His bowel and bladder habits are normal. He smokes about 30 sticks/day for 25 years.

On examination, general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is superior vena cava obstruction.

Q. What do you think the **cause** of SVC obstruction in this case?

A. Mention according to the age of the patient:

- In elderly or middle aged—causes are bronchial carcinoma, lymphoma
- In young or early age—common cause is lymphoma.

Q. Tell one **single investigation** which will help the diagnosis of SVC obstruction.

A. Chest X-ray (which may show bronchial carcinoma and lymphoma).

Q. What **investigations** should be done in SVC obstruction?

A. As follows:

1. Chest X-ray
2. CBC, ESR
3. Sputum for malignant cells
4. CT or MRI of chest
5. Others (according to suspicion of cause or physical findings):
   - ♦ If palpable lymph nodes FNAC or biopsy
   - ♦ Bronchoscopy and mediastinoscopy, venography and occasionally thoracotomy may be needed
   - ♦ Echocardiography in some cases.

RELATED QUESTIONS AND ANSWERS

Q. What **physical findings** did you look for to find out the cause of SVC obstruction?

A. As follows:

- ❖ Chest (bronchial carcinoma)
- ❖ Lymph nodes (lymphoma and metastasis)
- ❖ Liver and spleen (lymphoma)
- ❖ Clubbing, nicotine stain (bronchial carcinoma)
- ❖ Thyroid (to see retrosternal thyroid).

Q. What are the **presentations** of SVC obstruction?

A. The patient may complain of:

- ❖ Breathlessness, cough, hoarseness of voice and dysphagia
- ❖ Flushing, red, puffy and edematous face
- ❖ Headache (early morning), which is severe with coughing. May be syncope, dizziness or blackout, stupor, seizure (due to increased intracranial pressure)
- ❖ Symptoms are aggravated on lying down or bending forward (indicates mediastinal involvement)
- ❖ The patient may have stridor (tracheal compression), hoarseness of voice (recurrent laryngeal nerve involvement), Horner's syndrome (cervical sympathetic chain involvement).

Features of mediastinal compression—according to the involvement of structure:

1. Trachea: breathlessness, cough, stridor.
2. Esophagus: Dysphagia.
3. Bronchus: Features of collapse of lung.
4. Recurrent laryngeal nerve: Hoarseness of voice, bovine cough.
5. Phrenic nerve: Breathlessness (X-ray chest shows raised diaphragm).
6. Cervical sympathetic chain involvement: Horner's syndrome.
7. SVC:
   - ♦ Face is puffy, edematous and red
   - ♦ Neck is swollen with engorged, non-pulsatile neck veins
   - ♦ Visible tortuous veins in chest wall and abdomen, flow is downwards
   - ♦ Upper limbs are edematous with prominent engorged veins.

Q. What are the **causes of death** in SVC obstruction?

A. Death is due to:

- ❖ Respiratory obstruction
- ❖ Intracranial hemorrhage.

Q. What are the **causes of SVC obstruction?**

A. As follows:

1. Bronchial carcinoma (common cause, in 75%)
2. Lymphoma (early age, also in elderly)
3. Other causes:
   - Retrosternal thyroid
   - Thymoma
   - Mediastinal fibrosis (its causes include idiopathic, radiation, methysergide used in migraine and histoplasmosis)
   - Metastasis to the mediastinum
   - Chronic constrictive pericarditis
   - Giant aortic aneurysm
   - Carcinoma of esophagus
   - Rarely thrombosis, invasion by malignancy, germ cell tumor.

Q. What is **Pemberton's test?**

A. On lifting the arms over the head for more then 1 minute, there is increased facial plethora or cyanosis, raised JVP (non-pulsatile) and inspiratory stridor.

Q. How will you **treat** the case?

A. Treatment is according to cause:

1. General treatment:
   - To relieve edema—intravenous frusemide, head should be raised, dexamethasone may be used
   - To relieve severe obstruction—expandable metallic stent may be used (placed in SVC) as palliative measure. Venoplasty may be considered
   - Anticoagulant may be given, if needed
   - Ventilatory support, if needed.
2. Treatment of cause:
   - The most common cause is bronchial carcinoma. Radiotherapy in non-small cell carcinoma and chemotherapy for small cell carcinoma.
   - If lymphoma—treat accordingly (usually chemotherapy).

Note Remember the following points:

- SVC obstruction of recent onset is likely to be due to malignancy
- SVC obstruction of long-standing is due to nonmalignant origin.

DIFFUSE PARENCHYMAL LUNG DISEASE (DPLD)

CHIEF COMPLAINTS

- Breathlessness for … months
- Cough for … months
- Weight loss for ... months.

HISTORY

History of present illness: According to the statement of the patient, he was alright … months back. Since then, he has been suffering from frequent cough which is usually non-productive, but sometimes with scanty mucoid expectoration. Cough is aggravated on exposure to dust and fume. He also complains of breathlessness. Initially, it was present during moderate to severe exertion, but for the last ... months, it is progressively increasing, becoming worse with mild exertion such as going to toilet, dressing, etc. There is no history of orthopnea or paroxysmal nocturnal dyspnea. He does not give any history of chest pain, hemoptysis, fever, joint swelling or pain, skin rash, oral ulcer. For the last ... months, he is experiencing malaise, marked loss of appetite and body weight. His bowel and bladder habits are normal. He denies any history of contact with birds at home or at work or with tuberculosis patient.

History of past illness: Nothing significant.

Family history: Nothing significant.

Personal history: He smokes about 15 sticks per day for 30 years, nonalcoholic.

Socioeconomic history: He works in a pillow shop where his job involves sorting cotton and making pillows, blankets, etc.

Drug history: He used to take cough syrup, salbutamol, aminophylline etc, for his cough.

GENERAL EXAMINATION

- The patient is dyspneic
- There is central cyanosis involving tongue, lips and finger tips
- Generalized clubbing is present involving all the fingers and toes. But no hypertrophic osteoarthropathy
- He is mildly anemic
- No jaundice, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- Pulse: 78/min
- BP: 120/80 mm Hg
- Respiratory rate: 30/min
- Temperature: Normal.

SYSTEMIC EXAMINATION

Respiratory System

Inspection:

- Chest expansion on both sides is reduced symmetrically.

Palpation:
- Trachea is central in position
- Apical beat is in left 5th intercostal space, just medial to the midclavicular line, normal in character
- Vocal fremitus is normal on both sides.

Percussion:
- Percussion note is resonant over both lung fields
- Upper border of liver dullness is in right 4th intercostal space in midclavicular line
- Area of cardiac dullness is normal.

Auscultation:
- Breath sound is vesicular with prolonged expiration
- Bilateral basal end-inspiratory fine crepitations (like unfastening of Velcro) unaltered by coughing is present
- Vocal resonance is normal.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 45 years old, worker in a pillow shop, normotensive, nondiabetic, smoker, hailing from …, presented with frequent cough for ... months, which is usually non-productive, but sometimes with scanty mucoid expectoration. Cough is aggravated on exposure to dust and fume. He also complains of breathlessness. Initially, it was present during moderate to severe exertion, but for the last ... months, it is progressively increasing, becoming worse with mild exertion such as going to toilet, dressing, etc. There is no history of orthopnea or paroxysmal nocturnal dyspnea. He does not give any history of chest pain, hemoptysis, fever, joint swelling or pain, skin rash, oral ulcer. For the last ... months, he is experiencing malaise, marked loss of appetite and body weight. His bowel and bladder habits are normal. He denies any history of contact with birds at home or at work or with tuberculosis patient. He smokes about 15 sticks per day for 30 years. He used to take cough syrup, salbutamol, aminophylline, etc. for his cough. There is no family history of such illness.

On examination – general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is DPLD (likely to be IPF).

Q. What are your **differential diagnoses?**

A. As follows:
- Bilateral bronchiectasis
- Fibrosis of the lung due to other causes
- Chronic heart failure.

Q. **Why not** pulmonary edema?

A. From the history, there is no orthopnea or PND or history suggestive of any cardiac disease. On examination, there is generalized clubbing which is against pulmonary edema.

Also, in pulmonary edema, crepitations are usually fine, both present in inspiration and expiration and altered by coughing. But in case of DPLD, it is usually end inspiratory coarse crepitations, unaltered by coughing.

Q. What **history did you take** to diagnose DPLD?

A. As follows:

- Onset of the disease—acute or chronic
- History of connective tissue disease like rheumatoid arthritis, systemic sclerosis, dermatomyositis, SLE
- History of drugs
- Occupational and environmental history.

Q. What are the causes of **bilateral basal crepitations?**

A. As follows:

- LVF (fine crepitation, may be altered by coughing, has other evidences of LVF)
- Bilateral brochiectasis (crepitations both in inspiration and expiration, altered by coughing)
- DPLD.

Q. What are the causes of **clubbing with bilateral basal crepitations?**

A. As follows:

- Bilateral brochiectasis
- DPLD.

Q. What **investigations** should be done in IPF (or DPLD)?

A. As follows:

1. Full blood count (shows different changes in different diseases):
   - ESR may be high (polycythemia is rare)
   - Lymphopenia (in sarcoidosis)
   - Eosinophilia (in pulmonary eosinophilia and drug reactions).
   - Neutrophilia (in hypersensitivity pneumonitis).
2. X-ray chest: Initially ground glass appearance, bilateral reticulonodular shadow mainly in lower zone. Lung size may be reduced, diaphragm may be raised. In advanced stage, there may be a honeycomb appearance.
3. HRCT: Helpful in early diagnosis, even when chest X-ray is normal. Changes are usually bilateral, peripheral and mainly in the lower lobes. There are patchy subpleural reticular abnormality with minimal or no ground glass changes, honeycomb (thick walled cysts 0.5 to 2 cm in terminal and respiratory bronchioles) and traction bronchiectasis.
4. Pulmonary function tests:
   - Restrictive pattern (FVC and FEV_1 are proportionately low, and ratio is normal or high).
   - Lung volumes are reduced (may be paradoxically preserved in patient with concomitant emphysema).
   - Reduced carbon monoxide (CO) transfer.
   - Peak flow rate may be normal.
5. Arterial blood gas: Hypoxemia with normal or low P_aCO_2 (due to hyperventilation).
6. Bronchoscopy: Bronchoalveolar lavage shows increased number of cells particularly neutrophils and macrophages. There may be increased lymphocytes in sarcoidosis, extrinsic allergic alveolitis and drug induced lung disease. Transbronchial lung biopsy may be needed for confirmation.
7. Others (according to suspicion of cause):
   - CRP may be raised
   - LDH (high level indicates disease activity in DPLD)
   - For sarcoidosis: Calcium may be elevated. Urinary calcium excretion and liver biopsy may be useful. Serum ACE is an indicator of disease activity. Gallium scanning may be done
   - For autoimmune diseases: Rheumatoid factor and anti-CCP antibodies. RA test and ANA are positive in 30% cases (in low titer)
   - Hypergammaglobulinemia.

8. For confirmation, lung biopsy is the definitive investigation. It is done in selected cases if diagnosis is uncertain. Biopsy is done in the following methods:
   - Transbronchial biopsy
   - Video assisted thoracoscopic (VATS) lung biopsy
   - Open lung biopsy in some cases.

Note

Lung biopsy is not a routine investigation. Typical clinical features and high-resolution CT (HRCT) are sufficient for diagnosis. However, lung biopsy is strongly indicated in young patient.

RELATED QUESTIONS AND ANSWERS

Q. What is **DPLD**?

A. DPLD are a heterogenous group of diseases characterized by diffuse lung injury and inflammation that can progress to lung fibrosis. Previously, it was called interstitial lung disease (ILD).

Q. **Why** is it called DPLD?

A. The term DPLD is preferred than ILD, because the pathological lesion involves the alveoli along with interstitium.

Q. What are the **stages** of DPLD?

A. As follows:
- Stage of ground glass opacity
- Stage of reticulonodular shadow
- Stage of streaky fibrosis
- Stage of honeycombing.

Q. **Classify** DPLS.

A. Six groups:
1. Granulomatous DPLD (e.g sarcoidosis).
2. Granulomatous DPLD with vasculitis (e.g. Wegener's granulomatosis, Churg Strauss syndrome, microscopic vasculitis).
3. Idiopathic interstitial pneumonia (IIP):
   a. Idiopathic pulmonary fibrosis (IPF, also called usual interstitial pneumonia—UIP. It was previously called cryptogenic fibrosing alveolitis 90%)
   b. Idiopathic interstitial pneumonia other than IPF (10%)
      - Desquamated interstitial pneumonia
      - Acute interstitial pneumonia
      - Nonspecific interstitial pneumonia
      - Respiratory bronchiolitis
      - Cryptogenic organizing pneumonia (COP, also called BOOP—bronchiolitis obliterans organizing pneumonia)
      - Lymphocytic interstitial pneumonia.
4. Pulmonary autoimmune rheumatic diseases (e.g. rheumatoid arthritis, SLE).
5. Drugs (busulfan, bleomycin, methotrexate, nitrofurantoin, amiodarone).
6. Other forms of DPLD, as for example histiocytosis X (Langerhans' cell histiocytosis), Goodpasture's syndrome, idiopathic pulmonary hemosiderosis, diffuse alveolar hemorrhage, lymphangioleiomyomatosis, pulmonary alveolar proteinosis.

Q. What are the **presentations** with IPF?

A. Patient is usually elderly, uncommon < 50 years

- Cough, usually dry
- Progressive breathlessness, usually exertional
- Arthralgia, cyanosis and finger clubbing (20 to 50% cases).

Q. What is the mechanism of **end-inspiratory crepitations** in IPF?

A. In IPF, alveoli remain collapsed. During forceful inspiration, sudden opening of collapsed alveoli produces coarse crepitations.

Q. What are the **diagnostic criteria** of IPF?

A. As follows:

Major criteria:

1. Exclusion of other known causes of DPLD, such as certain drug toxicities, environmental exposures, and connective tissue diseases.
2. Abnormal pulmonary function studies that include evidence of restriction.
3. Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scans.
4. Transbronchial lung biopsy or BAL showing no features to support an alternative diagnosis.

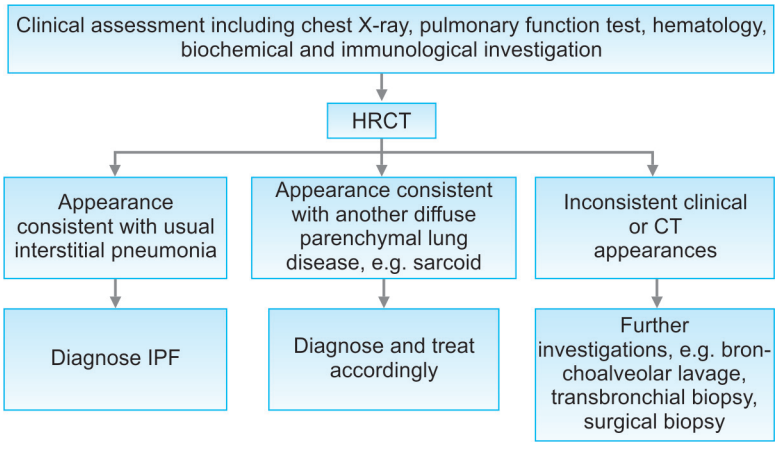
Minor criteria:

1. Age >50 year, male, smoker.
2. Insidious onset of otherwise unexplained dyspnea on exertion.
3. Duration of illness >3 months.
4. Bibasilar, inspiratory crackles (dry or "Velcro"-type in quality).

In the immunocompetent adult, the presence of all of the major diagnostic criteria as well as at least three of the four minor criteria increases the likelihood of a correct clinical diagnosis of IPF.

Q. How will you **investigate** a case of DPLD?

A. As follows:


Clinical assessment including chest X-ray, pulmonary function test, hematology, biochemical and immunological investigation
HRCT
Appearance consistent with usual interstitial pneumonia
Appearance consistent with another diffuse parenchymal lung disease, e.g. sarcoid
Inconsistent clinical or CT appearances
Diagnose IPF
Diagnose and treat accordingly
Further investigations, e.g. bronchoalveolar lavage, transbronchial biopsy, surgical biopsy

Q. What are the **conditions mimicking** DPLD?

A. As follows:

- Infections: Viral pneumonia, TB, fungal infection, *Mycoplasma pneumoniae*, *Pneumocystis jirovecii* and parasites (e.g. filariasis).
- Malignancy: Leukemia, lymphoma, multiple metastases, lymphatic carcinomatosis, bronchoalveolar carcinoma.

- Pulmonary edema.
- Aspiration pneumonitis.

Q. How to **treat** IPF?

A. As follows:

1 Prednisolone 0.5 mg/kg with azathioprine 2 to 3 mg/kg is recommended in:
   - Highly symptomatic
   - Rapidly progressive disease
   - Ground glass opacity on CT scan
   - Sustained > 50% fall of FVC over 3 to 6 months.

2 Antifibrotic therapy (on trial):
   - Interferon γ 1b
   - Pirfenidone
   - Sildenafil
   - Bosentan
   - Etanercept (biological agent)
   - Thalidomide
   - N- acetyl cysteine.

3 Single lung transplantation in young patient at advanced stage. Survival is 1 year in 60% cases.

Prednisolone is given for at least 2 months and then tapered to a maintenance dose of 10 to 12.5 mg daily.

Q. What is the **prognosis** of IPF?

A. Usually 3 to 5 years survival in 50% cases (65% in steroid responder and 25% in steroid non-responder).

Q. What are the **complications** of IPF?

A. As follows:

- Pulmonary hypertension and cor pulmonale.
- Respiratory failure
- Others—infection and bronchial carcinoma.

Q. What are the **differences** between IPF (UIP) and COP (BOOP)?

A. As follows:

Features	IPF (UIP)	COP (BOOP)
1. Age	Elderly (55 to 60 years), slightly more in male	Adult
2. Smoking	Associated	Not associated
3. Onset	Insidious	Abrupt
4. Constitutional symptoms (fever, fatigue and weight loss)	Unusual	Common
5. Finger clubbing	Present	Absent
6. ESR	May be normal	Markedly increased

Contd...

Contd...

7. Lung function tests	Restrictive with reduced diffusing capacity	Restrictive but concomitant obstruction in 25% cases
8. Chest X-ray	Diminished lung volume	Normal lung volume
9. ANA, RA tests	Positive in 30%	Negative
10. Biopsy	Usually not required for diagnosis	Required. It typically shows buds of connective tissue (Masson's bodies)
11. Response to corticosteroid	Poor	Good in 2/3rd patients
12. Prognosis	Poor, median survival 3 to 5 years	Good if responsive to steroid Relapse are common

Q. What is **Hamman-Rich syndrome?**

A. It is a type of acute form of IPF, occurs in a small proportion of cases.

Q. What are the **restrictive** and **obstructive** airway diseases? What are the **differences**?

A. As follows:

- Restrictive: DPLD, ankylosing spondylitis and kyphoscoliosis.
- Obstructive: Emphysema, chronic bronchitis and bronchial asthma.

The differences are:

Features	Restrictive	Obstructive
1. Both FEV_1 and FVC	Proportionately reduced	FEV_1 is markedly reduced and FVC also reduced
2. Ratio between FEV_1 and VC	Normal	Reduced
3. RV	Reduced or normal	Increased
4. TLC	Reduced	Increased
5. Ratio between RV and TLC	Normal or slightly increased	Markedly increased

CYSTIC FIBROSIS

CHIEF COMPLAINTS

- Severe cough for … days
- Breathlessness for … days
- Fever for … days.

HISTORY

History of present illness: According to the statement of the patient, she was alright … days back. Since then, she has been suffering from severe cough which is productive with moderate amount of whitish sputum, which is more in the morning after waking from sleep. She also noticed scanty amount of blood in sputum once. She is also experiencing breathlessness for … days which is not related to physical exertion. There is no history of orthopnea or paroxysmal nocturnal dyspnea. The patient also complains of fever for … days which is high grade, intermittent, not associated with chill or rigor and subsides with sweating after taking paracetamol. Her appetite, bowel and bladder habits are normal. There is no history of chest pain, headache, sore throat, skin rash. There is no history of contact with tuberculosis patient.

History of past illness: She has been suffering from recurrent respiratory infection and bronchial asthma since her childhood. She took inhaler regularly for asthma. She also had intermittent abdominal pain and loose, bulky stool.

Family history: One of her sister had similar problems with recurrent respiratory tract infection and died at the age of 18 years.

Personal history: Mention according to the patient's statement.

Socioeconomic history: Mention according to the patient's statement.

Drug history: She took paracetamol, cough syrup, and salbutamol inhaler.

GENERAL EXAMINATION

- The patient is slightly emaciated.
- There is generalized clubbing involving both toes and fingers, but no hypertrophic osteoarthropathy.
- No anemia, jaundice, cyanosis, edema, koilonychia or leukonychia.
- No thyromegaly or lymphadenopathy.
- Pulse: 84/min.
- BP: 120/70 mm Hg.
- Respiratory rate: 26/min.
- (Examination of the sputum cup: Always look at the cup at the side of the patient, if any).

SYSTEMIC EXAMINATION

Respiratory System

Inspection:

- Chest movement slightly restricted (mention where). Or, no abnormality.

Palpation:
- Trachea—Central
- Apex beat—In left 5th intercostal space 9 cm from the midsternal line
- Vocal fremitus—Slightly increased on both base
- Chest expansion—Normal.

Percussion:
- Percussion note—Normal
- Liver and cardiac dullness—In normal area.

Auscultation:
- Breath sound—Normal vesicular (may be bronchial over the involved area)
- There are multiple coarse crepitations on the base of both lungs, both in inspiration and expiration, reduced (or disappeared) after coughing
- Vocal resonance—Slightly increased (mention where).

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Ms …, 15 years old, student, normotensive, nondiabetic, nonsmoker, hailing from …, presented with severe cough for … days which is productive with moderate amount of whitish sputum, which is more in the morning after waking from sleep. She also noticed scanty amount of blood in sputum once. She is also experiencing breathlessness for … days which is not related to physical exertion. There is no history of orthopnea or paroxysmal nocturnal dyspnea. The patient also complains of fever for … days which is high grade, intermittent, not associated with chill or rigor and subsides with sweating after taking paracetamol. Her appetite, bowel and bladder habits are normal. There is no history of chest pain, headache, sore throat, skin rash. There is no history of contact with tuberculosis patient. She has been suffering from recurrent respiratory infection and bronchial asthma since her childhood. She took inhaler regularly for asthma. She also had intermittent abdominal pain and loose, bulky stool. One of her sister had similar problems with recurrent respiratory tract infection and died at the age of 18 years. She took paracetamol, cough syrup, and salbutamol inhaler.

On examination – general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is bronchiectasis, more likely due to cystic fibrosis.

Q. What is **cystic fibrosis**?

A. Cystic fibrosis is an autosomal recessive disease characterized by abnormal transport of chloride and sodium ions across an epithelium, causing thick, viscous secretions and leading to bronchopulmonary infection and pancreatic insufficiency.

There is an abnormality in the gene encoding a chloride ion channel in the nasal epithelium, lungs, salivary glands, pancreas, intestine and bile ducts.

Prevalence is 1/2,500.

Q. What are the **clinical features** of cystic fibrosis?

A. As follows:

1. Neonate: Failure to thrive, meconium ileus, rectal prolapse.
2. Children and young adult—
   - Respiratory: Cough, wheeze, recurrent infection, bronchiectasis, lung abscess, pneumothorax, lobar collapse, hemoptysis, respiratory failure, cor pulmonale, asthma, otitis media, sinusitis, nasal polyps, etc.

- Abdominal: Diabetes mellitus, steatorrhea, malabsorption, cholesterol gallstone, secondary biliary cirrhosis and portal hypertension, distal intestinal obstruction syndrome (meconium ileus equivalent syndrome). There is increased incidence of peptic ulceration and gastrointestinal malignancy.
- Others—male infertility (due to failure of development of vas deferens and epididymis), delayed puberty and skeletal maturity, arthritis, osteoporosis, vasculitis, hypertrophic pulmonary osteoarthropathy, clubbing, stress incontinence due to repeated forced cough. About 20% of female with cystic fibrosis are infertile.

Q. What is **distal intestinal obstruction syndrome** (meconium ileus equivalent syndrome)?

A. It is a form of small intestinal obstruction occurring during infancy and onwards in a patient with cystic fibrosis, resulting from a combination of steatorrhea and viscid intestinal secretions, causing fecal impaction in ascending colon or in ileocecal junction.

Q. How to **diagnose** a case of cystic fibrosis?

A. It is based on clinical history and:

- Family history of cystic fibrosis.
- Sweat test—high sweat sodium and chloride concentration over 60 mmol/L.
- Blood DNA analysis of gene defect.
- Radiological features of bronchiectasis.
- Absent vas deferens and epididymis.
- Blood immunoreactive trypsin levels (for screening purpose).

Q. What other **investigations** should be done in a patient with cystic fibrosis?

A. As follows:

- Blood—CBC, liver function tests, creatinine, electrolyte, coagulation study.
- Vitamin A, D, E levels.
- Glucose tolerance test (annually).
- Bacteriology—cough swab, sputum culture.
- X-ray chest (hyperinflation, bronchiectasis).
- Ultrasonogram of whole abdomen (fatty liver, cirrhosis, chronic pancreatitis).
- Spiromery (obstructive defect).
- Aspergillus serology or skin test.
- Fecal fat analysis.

Q. How to **treat** cystic fibrosis?

A. As follows:

1. General care:
   - Nutritional support
   - Fat soluble vitamin supplement
   - Strict glucose control
   - Smoking cessation
   - Vaccination with influenza and pneumococcal vaccines
2. For respiratory problems:
   - Regular physiotherapy (postural drainage, active cycle techniques, forced expiratory techniques, etc.).
   - Antibiotic for acute infective exacerbations (oral or IV) and prophylactically (oral flucloxacillin or nebulized colomycin or torbramycin).

- Symptomatic relief by mucolytic, bronchodilators, inhaled corticosteroid. In some patients, inhalation of recombinant DNAse or hypertonic saline may give some relief.
- Oxygen therapy, as needed.
- Pulmonary rehabilitation.

3. For advanced lung disease: Oxygen, diuretics (for cor pulmonale), non-invasive ventilation, lung or heart-lung transplantation.
4. For abdominal problems:
   - Pancreatic enzyme replacement.
   - If acute abdomen due to intestinal obstruction—nothing by mouth, IV fluid and nasogastric suction should be given. Acetylcysteine given intravenously or through the nasogastric tube has been shown to be useful in resolving bowel obstruction.
   - Ursodeoxycholic acid for impaired liver function.
   - Liver transplantation may be needed in cirrhosis.
5. Others: Treatment for osteoporosis, arthritis, sinusitis, vasculitis and infertility.
6. Genetic counseling.

Note Remember the following points:

- Diagnosis of cystic fibrosis should be suspected in any young patient who presents with chronic respiratory and chronic gastrointestinal problem.
- Gastrointestinal problems, malabsorption and diabetes mellitus in patient with cystic fibrosis is due to pancreatic insufficiency.
- Fecal elastase is used as a screening test for exocrine pancreatic dysfunction.
- *P. aeruginosa* is the most common organism, causing recurrent respiratory infection.
- Prognosis—median survival is now over 30 years.

CHAPTER 3

Cardiovascular System

Usually, few cases are selected as long case. Most are selected as short cases. Occasionally, combinations of multiple valvular lesions are selected. Prototype of a single case and also common combinations are described in this chapter.

- **Mitral Stenosis 162**
- **Mitral Regurgitation 175**
- **Mixed Mitral Stenosis with Mitral Regurgitation 181**
- **Aortic Stenosis 183**
- **Aortic Regurgitation 189**
- **Mixed Aortic Stenosis and Regurgitation 196**
- **Congestive Cardiac Failure with Valvular Lesion 199**
- **Hypertension 208**
- **Subacute Bacterial Endocarditis 217**
- **Rheumatic Fever 224**
- **Eisenmenger's Syndrome 231**
- **Tetralogy of Fallot 235**
- **Ventricular Septal Defect (VSD) 240**
- **Atrial Septal Defect (ASD) 244**
- **Patent Ductus Arteriosus (PDA) 248**
- **Coarctation of Aorta 252**
- **Hypertrophic Cardiomyopathy 257**

While taking history, remember to describe the common symptoms related to cardiac disease (see page 30). Common symptoms related to cardiac diseases are:

- Dyspnea (difficulty in breathing)
- Chest pain
- Palpitation
- Edema.

Other symptoms may occur secondarily due to the involvement of other anatomical systems of the body. Examples are as follows:

Respiratory:
- Cough (pulmonary edema)
- Hemoptysis (due to pulmonary hypertension).

Renal:
- Reduction of urine output (in CCF).

Gastrointestinal tract (GIT):
- Anorexia, nausea (in congestive cardiac failure (CCF))
- Pain abdomen (hepatomegaly in CCF, vascular occlusion due to embolism).

Neurological:
- Syncope (occurs in aortic stenosis, arrhythmia, hypotension)
- Stroke (may occur in atrial fibrillation, hypertension, SBE, mitral stenosis due to cerebral embolism).

All these symptoms should be enquired during taking the history.

Note Remember the following:

Remember, in any cardiac case, patient's complaint or presentations are almost similar. Signs are written separately in individual cases.

MITRAL STENOSIS

After mentioning the name, age, sex, occupation, etc. as in proforma (written in the beginning), proceed as follows:

CHIEF COMPLAINS

- Breathlessness for … months
- Palpitation for … months
- Cough ... months
- Weakness for … months.

HISTORY

History of present illness: According to the patient's statement, he has been fit and well. However for the … months, he has been suffering from occasional breathlessness. Initially, the patient felt breathless during moderate to severe exertion, but for the last few weeks, it has been increasing progressively. Now he feels breathless even on mild exertion. Occasionally, he experiences nocturnal breathlessness, usually at late hours of night, for which he has to get up from sleep, walk and take deep breath to be comfortable.

There is no history of breathlessness on lying flat (orthopnea).

The patient also complains of occasional palpitation with mild exertion, even while going to toilet or dressing. He also complains of cough with sputum, which is mucoid in nature, but not associated with hemoptysis. For the last … months, he feels weak and fatigued.

There is no history of chest pain, swelling of legs, syncope, loss of consciousness, hoarseness of voice or difficulty in swallowing.

History of past illness: The patient suffered from rheumatic fever in his childhood (arthritis involving the big joints which were fleeting in nature), but there was no abnormal limb movements (even if no history of rheumatic fever or chorea, mention it. History of rheumatic fever may be absent in 40% case).

Family history: Both of his parents are in good health. His two brothers and two sisters are also in good health. There is no such illness in his family.

Personal history: He is a student, nonsmoker, nonalcoholic (mention if anything significant).

Socioeconomic history: He is from a middle class family, living in a small house with good sanitation and water supply facilities.

Drug history: He was taking injection Benzylpenicillin for few years, but has now stopped. He was treated by a community physician, but cannot recall the medications.

GENERAL EXAMINATION

- Appearance: Ill looking. (If malar flush, called mitral facies, is present, mention it.)
- Built: Normal
- Nutrition: Average
- Decubitus: On choice
- Anemia: Mild
- No jaundice, cyanosis, edema, clubbing, koilonychia, leukonychia
- No lymphadenopathy or thyromegaly

- Pulse: 88/min, low volume, regular in rhythm
- BP: 100/70 mm Hg
- Temperature: 98.8ºF.

SYSTEMIC EXAMINATION

Cardiovascular System

- **Pulse:** 88/min, low volume and regular in rhythm, normal character, no radio-femoral and radio-radial delay. Condition of vessel wall is normal.
- **Neck veins**: not engorged.
- **Blood pressure:** 100/70 mm Hg.

Precordium

Inspection:

- Visible cardiac impulse in mitral area (if other impulse, mention it)
- No deformity or scar-mark (mention if there is valvotomy scar or midline scar for valve replacement).

Palpation:

- Apex beat: In left 5th intercostal space ... cm from midline, tapping in nature
- Thrill: There is apical thrill, diastolic in nature
- Palpable P_2: Absent
- Left parasternal lift: Absent
- Epigastric pulsation: Absent (if present, mention it).

Auscultation:

- First heart sound: Louder in all the areas, more prominent in mitral area
- Second heart sound: Normal in all the areas (P_2 is loud in pulmonary area, if pulmonary hypertension)
- Murmur: There is a mid diastolic murmur in mitral area, which is low pitched, localized, rough, rumbling (LLRR), best heard with the bell of stethoscope, in left lateral position with breathing hold after expiration, with presystolic accentuation
- There is also opening snap, just medial to the mitral area.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr ..., 20-year-old, a college student, nonhypertensive, nondiabetic, nonsmoker, presented with breathlessness for … months, palpitation for … months, cough for ... months and weakness for … months. Initially, he felt breathless during moderate to severe exertion, but for the last few weeks, it is progressively increasing. Now he feels breathlessness even on mild exertion. Occasionally, he experiences paroxysmal nocturnal dyspnea but no history of orthopnea. The patient also complains of occasional palpitation with mild exertion, even while going to toilet or dressing. Cough is productive, with mucoid sputum, but not associated with hemoptysis. For the last … months, he feels weak and fatigued. There is no history of chest pain, swelling of legs, syncope, loss of consciousness, hoarseness of voice or difficulty in swallowing.

In his past medical history, there is history of rheumatic fever in his childhood. All the family members are in good health and there is no history of known genetic diseases. He was taking injection Benzylpenicillin for few years, but has now stopped. He was treated by a community physician but cannot recall the medications.

On general examination (see above).

On systemic examination (see above).

My diagnosis is: Chronic rheumatic heart disease with mitral stenosis.

(If signs of pulmonary hypertension are present, then add it with the above diagnosis).

Q. What are the main **points in favor** of your diagnosis?

A. The points in favor are:

- Apex beat is tapping in nature
- Diastolic thrill in mitral area
- Loud first heart sound
- Presence of MDM in mitral area with presystolic accentuation
- Presence of opening snap.

Q. What is the likely **cause** of MS?

A. Chronic rheumatic heart disease (always the most common cause).

Q. If there is **no** history of rheumatic fever, then what would be the cause?

A. Still it is likely to be rheumatic fever, because history of rheumatic fever may be absent in 40% cases. Rheumatic fever is the commonest cause of MS, rarely it may be congenital.

Q. Is there any evidence of pulmonary hypertension (PH)?

A. No.

Q. What are the **signs** of PH?

A. As follows:

- Palpable P_2
- Prominent 'a' wave in JVP
- Left parasternal heave (indicates RVH)
- Epigastric pulsation (indicates RVH)
- Loud P_2 on auscultation
- Early diastolic murmur (Graham Steel murmur due to pulmonary regurgitation).

Q. What are your **differential diagnoses?**

A. As follows:

- Tricuspid stenosis
- Left atrial myxoma
- Others: Ball valve thrombus in left atrium, cortriatum (a rare congenital disease).

Q. Why **not** this is tricuspid stenosis?

A. In TS, MDM is prominent in left lower parasternal edge, which increases during inspiration. Also, there may be other features such as raised JVP and signs of right heart failure.

Q. Why **not** this is left atrial myxoma?

A. In left atrial myxoma, physical signs and murmur change with posture. Also, there may be history of fever, weight loss, myalgia, arthralgia, skin rash, Raynaud's phenomenon (which are absent in this case). To be confirmed, 2D echocardiography should be done.

Q. What is **myxoma** of the heart? What are the **features**? How to **investigate** and **treat**?

A. It is the common primary tumor of heart, usually benign, may be pedunculated, polypoid, gelatinous, attached by a pedicle to the atrial septum. It may be sporadic and familial. It occurs in any age (third to sixth decade), and any sex (more in female).

Sites of origin:

- Left atrium (75%), near the fossa ovalis or its margin
- Right atrium, rarely from ventricles.

Clinical features: There are 3 groups of manifestations:

1. Obstructive features: Like MS, signs vary with posture. Occasionally, there is a low-pitched sound called tumor plop. There may be syncope or vertigo.
2. Embolic features either systemic or pulmonary embolism.
3. Constitutional features: Such as fever, malaise, weakness, loss of weight, myalgia, arthralgia, clubbing, skin rash, Raynaud's phenomenon.

Investigations:

- CBC: May be anemia, leukocytosis, polycythemia, high ESR, thrombocytopenia or thrombocytosis
- Hypergammaglobulinemia
- Chest X-ray (may be similar to MS)
- Echocardiogram: 2D or transesophageal
- CT scan or MRI may be done.

Treatment: Surgical excision. Recurrence may occur.

Note Remember the following:

Other tumors of the heart are rhabdomyoma and sarcoma. All are rare.

Q. What **investigations** should be done in mitral stenosis?

A. As follows:

- X-ray chest P/A view.
- ECG: "P" is bifid (P-mitrale. May be RVH, RAH, AF, etc).
- To confirm, echocardiogram (2D or preferably color doppler).
- Cardiac catheter may be done in some cases, specially when associated with other diseases (coronary artery disease, MS with MR, pulmonary artery pressure measurement).

Q. What are the **radiological features** of mitral stenosis?

A. As follows:

- Upper lobe veins are dilated (called upper lobe diversion, which is the early feature). Normally, ratio between upper and lower lobe veins is 1:3, which is altered to 1:1.
- Straightening of left border of heart (also called **mitralization**): It is due to fullness of pulmonary conus (due to dilated pulmonary artery) and filling of pulmonary bay (due to prominent left atrial appendage due to left atrial enlargement).
- Kerley's B lines (horizontal septal lines in costophrenic angle, which indicates pulmonary hypertension).
- Double shadow in right border of heart (due to enlarged left atrium).
- Widening of carina.
- Left bronchus is horizontal (due to enlarged left atrium).
- Pulmonary edema.
- Mottling or reticulonodular shadow due to pulmonary hemosiderosis.
- Calcified shadow of mitral valve (it is best seen in fluoroscopy).

Q. What is the **barium swallow** of esophagus (right anterior oblique view) finding?

A. Indentation of the esophagus due to enlarged left atrium (it is not done now a days, because echocardiogram is more diagnostic).

Q. What are the **echocardiogram findings** in mitral stenosis?

A. As follows:

- Thick mitral valve leaflet (with restricted opening), diastolic doming of anterior mitral leaflet and restricted movement of posterior mitral leaflet.
- Reduction of valvular area (narrow): Button like or funnel shaped.
- Calcification of valves (increased echogenecity).
- Shortening of chordae tendinae.
- Enlarged left atrium.
- Reduced rate of diastolic filling of left ventricle.
- Characteristic "M" shape movement of anterior leaflet normally seen in diastole is lost and the diastolic slope (EF) is reduced.
- Thrombus may be seen.

RELATED QUESTIONS AND ANSWERS

Q. If the patient with MS suddenly becomes **unconscious**, what is the likely cause?

A. CVD (cerebral infarction), usually with right sided hemiplegia. Usually CVD occurs when there is associated atrial fibrillation (AF).

Q. What may be the **cause of CVD** in this case?

A. Cerebral embolism (involving lenticulostriate branch of the left middle cerebral artery, causing infarction of the internal capsule).

Q. Why **syncope** may occur in MS?

A. Due to reduction of cardiac output. Also, may be due to atrial fibrillation with fast ventricular rate, pulmonary hypertension, pulmonary embolism, ball valve thrombus, cerebral embolism.

Q. What is the cause of **hemoptysis** in MS?

A. Rupture of pulmonary or bronchial veins associated with pulmonary hypertension (pulmonary apoplexy). Also hemoptysis may be due to pulmonary infarction.

Q. What is **paroxysmal nocturnal dyspnea** (PND)?

A. Paroxysmal breathlessness usually at night, which awakens the patient from sleep with a feeling of suffocation and choking sensation. The patient sits, stands up or open the windows for fresh air. It is due to pulmonary edema, and indicates early LVF or left atrial failure.

Q. What are the **causes** of PND?

A. The causes are as follows:

- Venous return increases while lying down.
- Mobilization of edema fluid from extravascular to intravascular compartment in supine position.
- Low adrenergic drive at sleep.
- Heart rate increases during rapid eye movement (REM) sleep.
- Vital capacity is reduced in supine position.
- Left atrial pressure is elevated and PaO_2 is reduced during sleep.
- Abdominal contents are also pushed up giving pressure on diaphragm.

Q. What are the **causes** of mid diastolic murmur (MDM)?

A. As follows:

- Mitral stenosis
- ASD (due to increased flow through tricuspid valve)
- Tricuspid stenosis
- Left atrial myxoma
- Austin-Flint murmur in aortic regurgitation
- Carey Coomb's murmur (a soft MDM due to mitral valvulitis in acute rheumatic fever).

Q. What are the characters of **Austin-Flint murmur** in aortic regurgitation?

A. As follows:

- It is not associated with loud first heart sound or presystolic accentuation
- No diastolic thrill
- No opening snap
- Patient will have features of aortic regurgitation.

Note Remember the following:

These features are present in organic MS.

Q. What is **Lutembacher's syndrome**?

A. Combination of ASD with rheumatic MS (it occurs in 4% cases of ASD).

Q. Why the apex beat is **tapping**?

A. It is the accentuated, palpable 1st heart sound.

Q. When and why the **pre-systolic accentuation** is present?

A. It is present only if there is sinus rhythm. It is due to atrial systole, which increases the flow across the stenosed mitral valve from left atrium to left ventricle, causing accentuation or loudness of the murmur. It is absent, if there is atrial fibrillation.

Q. What is **opening snap**? What is the **mechanism**?

A. It is a short, sharp high pitched sound, heard immediately after 2nd heart sound (during diastole), produced by sudden opening of mitral valve, due to raised left atrial pressure.
Opening snap is usually found in MS. (Rarely, it may be found in TS, severe MR, etc.).

Q. What is the **significance** of opening snap?

A. As follows:

- It indicates that the valve cusp is still mobile
- It is absent when the valve is calcified
- The gap between second heart sound and opening snap indicates the severity of MS. The diminishing gap indicates severe MS
- It is always due to organic MS.

Q. How to assess the **severity** of MS (is it severe)?

A. Normal area of mitral valve is 4 to 6 cm^2, if severe it may be <1 cm^2 (tight MS).

Signs of severe MS are:

- Pulse: Low volume
- 1st heart sound: Soft
- Opening snap: Nearer to the 2nd sound
- MDM: Prolonged
- Evidence of pulmonary hypertension and pulmonary congestion.

Q. How to assess the **pliable mitral valve**?

A. Short, sharp, accentuated first sound and presence of opening snap.

Q. What is the feature of **non-pliable** mitral valve?

A. Muffled first heart sound and no opening snap.

Q. What is **mitral facies**?

A. It is the rosy coloration of cheeks, may be bluish tinge, due to dilated capillaries and venules on the cheeks. It is not pathognomonic. It may be present in pulmonary hypertension and occasionally in normal person.

Q. Why there is **pulmonary hypertension in MS**?

A. Because of:

- Passive backward transmission of raised left atrial pressure
- Reflex pulmonary artery vasoconstriction
- Organic obliterative change in pulmonary vascular bed.

Q. What are the **complications** of MS?

A. As follows:

- Atrial fibrillation.
- Pulmonary edema (left atrial failure).
- Pulmonary hypertension leading to CCF.
- Left atrial thrombus with systemic embolism—commonly cerebral (cerebral infarction with hemiplegia), also in mesenteric, renal and peripheral.
- Ball valve thrombus (which is a big thrombus) may lead to sudden death.
- Hemoptysis.
- Pulmonary congestion, embolism, infarction.
- Ortner's syndrome (enlarged left atrium gives pressure on left recurrent laryngeal nerve, causing hoarseness of voice. It is rare).
- Dysphagia due to enlarged left atrium.
- Bronchitis and recurrent bronchopulmonary infection.
- Chest pain in 10% cases (due to pulmonary hypertension).
- Long standing MS may cause interstitial lung disease (due to prolonged pulmonary edema) and hemosiderosis.
- Infective endocarditis: Very rare (common in mitral regurgitation).

Q. How to **treat** MS medically?

A. As follows:

- Restrictive activity.
- Anticoagulant to reduce the risk of embolism.
- If atrial fibrillation: Digoxin, beta blocker, rate limiting calcium antagonsist (e.g. verapamil, diltiazem).
- If there is CCF: Diuretics, digoxin.
- Infective endocarditis is very unusual in MS. So, routine prophylaxis with antibiotic is not recommended.

Q. What are the indications of anticoagulant (warfarin) in MS?

A. As follows:

- Systemic and pulmonary embolism.
- Atrial fibrillation.
- Left atrial thrombus.
- Left ventricular systolic dysfunction.

Q. What are the **indications of surgery** in MS?

A. As follows:

- Symptomatic moderate or severe MS when balloon valvuloplasty is unavailable
- Moderate or severe MS with moderate or severe MR
- Recurrent thromboembolism
- Episodes of pulmonary edema without precipitating cause
- Associated atrial fibrillation which does not respond to medical therapy
- Pulmonary hypertension or recurrent hemoptysis
- Occasionally in pregnancy, with pulmonary edema (surgery may be done in second trimester as blood volume increases significantly with increased pulmonary pressure).

Q. What **surgery** is usually done?

A. As follows:

- Valvotomy (CMC—closed mitral commissurotomy, OMC—open mitral commissurotomy)
- Valvuloplasty (percutaneous balloon mitral valvuloplasty)—Treatment of choice
- Valve replacement.

Q. What are the **criteria for valvuloplasty**?

A. As follows:

- Significant symptoms
- Pure MS
- No or trivial MR
- Valve—Mobile, no calcification
- Left atrium—No thrombus.

Q. What are the **indications of valve replacement**?

A. As follows:

- Associated MR
- If the valve is calcified and rigid
- Thrombus in left atrium despite anticoagulation.

Q. What are the **complications** of surgery?

A. As follows:

- Mitral regurgitation
- Thromboembolism
- Restenosis.

Q. What is the **contraindication** of surgery in MS?

A. Active rheumatic carditis.

Q. How to **treat MS in pregnancy**?

A. As follows:

- Bed rest
- Correction of anemia
- Correction of nutrition
- If severe, symptomatic and tight MS—Mitral valvotomy may be done (usually in middle trimester)
- All patients should go into full term and cesarean section should be done
- Advice the patient to restrict number of pregnancy (1 to 2).

Note

Symptoms of MS are usually more marked in second trimester, which is due to increase in blood volume that increases pulmonary pressure. The symptoms improve in third trimester due to decrease in blood volume.

MITRAL STENOSIS WITH CONGESTIVE CARDIAC FAILURE (CCF)

Mitral stenosis may be associated with congestive cardiac failure. In such cases, **in addition to the history mentioned in mitral stenosis**, add the following:

- In the history, patient may complain of weakness, anorexia, nausea, vomiting, swelling of legs, pain in the right hypochondrium, etc.
- In physical finding, signs of CCF should be mentioned: Engorged and pulsatile neck veins, enlarged tender liver and dependent pitting edema (For details, see CCF on page 201).

Q. How to **treat** your case?

A. As follows:

- Complete rest.
- Restriction of salt and fluid.
- If breathlessness, oxygen therapy.
- Diuretics (frusemide, bumetanide, thiazide, spironolactone).
- If pulse rate is high: Digoxin may be given.
- Vasodilator drugs may be helpful (reduce afterload). Drugs are ARB, ACE inhibitor, nitrates.
- Treatment of mitral stenosis (such as valvotomy or valvuloplasty).

MITRAL STENOSIS WITH CARDIOVASCULAR DISEASE (CVD)

Mitral stenosis may be associated with CVD (cerebral embolism). In such case, the patient usually presents with unconsciousness or may be conscious and right sided hemeplagia.

- Physical findings are upper motor neuron science on the right side of the body (hypertonia, exaggerated reflects, extensor plantar response). For details, see CVD in neurology chapter.
- Usually there is atrial fibrillation (see below).

Q. What **investigations** should be done in such case?

A. As follows:

- As in mitral stenosis
- CT scan of brain (usually shows infarction).

Q. How to **treat** such case?

A. As follows:

- Treatment of atrial fibrillation
- Antiplatelet drugs: Aspirin, clopidogrel
- Anticoagulant: Warfarin.

MITRAL STENOSIS WITH ATRIAL FIBRILLATION (AF)

Mitral stenosis may be associated with atrial fibrilation. In such case, in addition to the history and signs of MS (as mentioned above), mention the signs of AF as follows:

- Pulse 110/min, irregularly irregular (in rhythm and volume)
- Pulse deficit is present (auscultate on heart and feel the radial pulse)
- No 'a' wave in JVP
- Variable intensity of first heart sound, no opening snap
- MDM is present, but no presystolic accentuation.

Q. Why **presystolic accentuation** is absent in AF?

A. Because in AF, atria contracts in an uncoordinated and ineffective manner.

Q. What do you think the **cause in this case**?

A. Chronic rheumatic heart disease.

Q. What are the **causes of irregularly irregular pulse**?

A. As follows:

- Atrial fibrillation
- Multiple ectopics
- Others: Atrial flutter with variable block, paroxysmal atrial tachycardia with variable block.

Q. How to **differentiate** atrial fibrillation and multiple ectopics at bedside?

A. By physical exercise. With exercise, ectopics will disappear. But atrial fibrillation will be more prominent or even worse. It is confirmed by ECG.

Q. What are the **causes of atrial fibrillation**?

A. As follows:

- Chronic rheumatic heart disease with valvular lesions, commonly mitral stenosis
- Coronary artery disease (commonly acute MI)
- Thyrotoxicosis
- Hypertension
- Lone atrial fibrillation (idiopathic in 10% cases)
- Others: ASD, chronic constrictive pericarditis, acute pericarditis, cardiomyopathy, myocarditis, sick sinus syndrome, coronary bypass surgery, vulvular surgery, acute chest infection (pneumonia), thoracic surgery, electrolyte imbalance (hypokalemia, hyponatremia), alcohol, pulmonary embolism.

Note Remember the following points:

- First 5 causes should always be mentioned sequentially at the top of the list.
- Mention the causes of atrial fibrillation according to the age of the patient in that particular long case (see below).

Q. If the patient is **young**, what are the **causes** of atrial fibrillation?

A. As follows:

- Chronic rheumatic heart disease with valvular lesions, commonly mitral stenosis
- Thyrotoxicosis
- Others—atrial septal defect (ASD), acute pericarditis, myocarditis, pneumonia.

Q. If the patient is **elderly**, what are the **causes** of atrial fibrillation?

A. As follows:

- Coronary artery disease (commonly acute myocardial infarction)
- Thyrotoxicosis

- Hypertension
- Lone atrial fibrillation (idiopathic in 10% cases)
- Others: See above (unusual or less in chronic rheumatic heart disease).

Q. What are the **complications** of atrial fibrillation?

A. As follows:

- Systemic and pulmonary embolism (systemic from left atrium and pulmonary from right atrium). Annual risk is 5% (1 to 12%).
- Heart failure.

Q. What is **lone atrial fibrillation?**

A. Lone atrial fibrillation means atrial fibrillation without any cause. Genetic predisposition may be responsible.

- 50% patients with paroxysmal atrial fibrillation and 20% with persistent or permanent atrial fibrillation have no cause and heart is normal.
- Lone atrial fibrillation usually occurs below 60 years of age.
- It may be intermittent, later may become permanent.
- Prognosis: Low risk of CVD (0.5% per year). Usually lifespan is normal.

Q. What is **atrial fibrillation?**

A. It is an arrhythmia where atria beat rapidly, chaotically and ineffectively, while the ventricles respond at irregular intervals, producing irregularly irregular pulse. Any conditions causing raised atrial pressure, increased atrial muscle mass, atrial fibrosis, inflammation and infiltration of the atrium can cause atrial fibrillation.

The atria usually fire impulse at the rate of 350 to 600/minute, ventricles respond at irregular intervals usually at the rate of 100 to 140/minute. Many of the atrial impulse reach the AV node in the refractory period. So, not all are conducted.

Q. What are the **types** of atrial fibrillation?

A. Three types:

- Paroxysmal: Discrete self-limiting episodes. May be persistent if underlying disease progresses.
- Persistent: Prolonged episode that can be terminated by electrical or chemical cardioversion.
- Permanent: Sinus rhythm cannot be restored with drug or DC shock.

Q. If a patient with atrial fibrillation is **unconscious**, what is the likely cause?

A. Cerebral embolism (usually with right sided hemiplegia).

Q. How to **treat** atrial fibrillation?

A. Aim of treatment is as follows:

- Control of heart rate
- Restoration of sinus rhythm and prevention of recurrence
- Treatment of primary cause.

Treatment (according to the type):

1. Paroxysmal atrial fibrillation:
   - If asymptomatic: Does not require any treatment, follow-up the case.
   - If troublesome symptoms are present: β-blocker. Other drugs—flecainide or propafenone may be given.
   - Amiodarone is effective in prevention.
   - Low dose aspirin to prevent thromboembolism.

- If bradycardia is present (in sinoatrial disease): Permanent over drive atrial pacing (60% effective).
- In some intractable cases: Radiofrequency ablation may be required, who does not have structural heart disease (70% effective).

2. Persistent atrial fibrillation:
   - Control of heart rate: β-blocker, digoxin or calcium channel blocker (verapamil, diltiazem). Combination of digoxin and atenolol may be used.
   - To control rhythm: DC cardioversion may be done safely. It may be repeated, if relapse occurs. Concomitant use of β-blocker or amiodarone may be used to prevent recurrence.
3. Permanent atrial fibrillation:
   - Control of heart rate: Digoxin, β-blocker, calcium channel blocker (verapamil or diltiazem).
   - In some cases: Transvenous radiofrequency ablation may be done (it induces complete heart block. So, permanent pacemaker should be given. This is known as "patch and ablate strategy").

Q. What is the **role of anticoagulant** in atrial fibrillation?

A. Usually, warfarin is given who are at risk of stroke. Target INR is 2 to 3. It reduces stroke in 2/3rd cases. Aspirin reduces stroke in 1/5th cases. Anticoagulation is indicated in patient with atrial fibrillation having risk factors for thromboembolism.

Risk factors for thromboembolism in atrial fibrillation:

- Previous ischaemic stroke or TIA
- Mitral valve disease
- Age over 65 years
- Hypertension
- Diabetes mellitus
- Heart failure
- Echocardiographic evidence of left ventricular dysfunction, left atrial enlargement or mitral anular calcification.

Risk groups with thromboembolism (nonrheumatic):

- Very high: Previous stroke or TIA (12%)
- High: Age > 65 years and one other risk factor (6.5%)
- Moderate: (i) Age > 65 years, no risk factor (4%), (ii) Age < 65 years, other risk factor (4%)
- Low: Age < 65 years, no risk factor (1.2%).

Note Remember the following points:

- In lone atrial fibrillation—aspirin may be given to prevent thromboembolism.
- Age < 65 years and young with no structural heart disease—aspirin may be beneficial. No warfarin.
- Target INR following anticoagulation is 2 to 3.

Assessment of risk of thromboembolism in atrial fibrillation—**CHADS score**:

- **C**ongestive cardiac failure (1 point)
- **H**ypertension (1 point)
- **A**ge > 75 (1 point)
- **D**iabetes mellitus (1 point)
- **S**troke or transient ischemic attack (2 points).

In **CHADS** score:

- Score 0 has a stroke risk of 1.9% per year.
- Score 6 correlates with 18.2% stroke risk per year.

For **prevention**:

- The patient with score 0 should get aspirin only
- The patient with score 1 should get warfarin or aspirin
- The patient with score 2 or more should get warfarin.

MITRAL REGURGITATION

History and general examination are similar to mitral stenosis (mention if other findings are present).

Cardiovascular System

- Pulse: 88/min, normal in volume, rhythm and character
- JVP: Not engorged
- Blood pressure: 130/85 mm Hg.

Precordium

Inspection:

- Visible cardiac impulse in mitral area.

Palpation:

- Apex beat: Shifted, in the left 6th intercostal space, ... cm from midline, diffuse, thrusting in character.
- Thrill: Present in left 6th intercostal space, systolic in nature.

Auscultation:

- 1st heart sound: Soft in mitral area, normal in other areas
- 2nd sound: Normal in all the areas
- 3rd heart sound: May be present
- There is a pansystolic murmur in mitral area, which radiates to the left axilla (reduced on inspiration and more on expiration).

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Present as mentioned in the chapter mitral stenosis. Also mention the physical findings as above.

My diagnosis is chronic rheumatic heart disease with mitral regurgitation.

Q. Why your diagnosis is MR?

A. Because:

- Systolic thrill in mitral area
- First heart sound is soft
- There is a PSM radiating to the left axilla.

Q. What do you think the cause in this case?

A. Chronic rheumatic heart disease, mitral valve prolapse.

Q. What are your differential diagnoses?

A. As follows:

- Tricuspid regurgitation (TR)
- Ventricular septal defect (VSD).

Q. Why not this is TR?

A. In TR, findings are:

- Pansystolic murmur is present in the left lower parasternal area, no radiation to axilla (No systolic thrill).
- Murmur is prominent on inspiration and less on expiration.
- Raised JVP with prominent "V" wave.
- Enlarged, tender and pulsatile liver.

Q. Why not this is VSD?

A. In VSD, findings are:

- Systolic thrill in left parasternal area (fourth or fifth intercostal space).
- Pansystolic murmur in left parasternal area (fourth or fifth intercostal space), no radiation.

Q. What investigations should be done in MR?

A. As follows:

- X-ray chest P/A view (cardiomegaly may be found)
- ECG (LVH, LAH)
- Echocardiogram, preferably color Doppler echocardiography
- Cardiac catheterization may be needed in some cases.

Q. What is mitral valve prolapse? What are the features? How would you treat?

A. It is also called Barlow's syndrome or floppy mitral valve. In this condition, a mitral valve leaflet (most commonly the posterior leaflet) prolapses into the left atrium during ventricular systole. It is one of the commonest causes of MR. It may be congenital anomaly or due to degenerative myxomatous changes. It may be associated with Marfan's syndrome, Ehler-Danlos syndrome, thyrotoxicosis, rheumatic or ischemic heat disease, atrial septal defect or hypertrophic cardiomyopathy.

Mitral valve prolapse is more common in thin, young women, may be familial. It may be present in healthy women in up to 10% cases. The most common symptom is atypical chest pain, usually in left submammary region and stabbing in quality. Rarely, it may be confused with anginal pain. There may be palpitation, dyspnea, fatigue, benign arrhythmia or rarely fatal ventricular arrhythmia. Embolic stroke and TIA are rare complications. Symptoms increases with aging.

On examination, the typical features are midsystolic click followed by late systolic murmur. Later, MR may develop and there is PSM. Two-dimensional echocardiography confirms the diagnosis.

Asymptomatic patient only needs reassurance, periodic echocardiography may be done. Atypical chest pain and palpitation are treated with β-blocker. Other antiarrhythmic drugs may be needed. If there is significant MR or AF, anticoagulation is indicated to prevent thromboembolism (aspirin may be given). If MR is severe, mitral valve repair or replacement should be done. Prophylaxis for infective endocarditis in most cases is not recommended. Overall prognosis is good.

RELATED QUESTIONS AND ANSWERS

Q. What are the causes of MR?

A. As follows:

- Chronic rheumatic heart disease
- Mitral valve prolapse
- Papillary muscle dysfunction (due to acute myocardial infarction)
- Infective endocarditis
- Trauma or mitral valvotomy

- Connective tissue diseases (RA, SLE, Marfan's syndrome, Ehler-Danlos syndrome)
- Ankylosing spondylitis
- Cardiomyopathy
- Secondary to left ventricular dilatation (hypertension, aortic valve disease)
- Rarely by drugs (such as fenfluramine, phentermine which are used to treat obesity).

Q. What are the **causes** of acute MR?

A. As follows:
- Acute myocardial infarction (due to rupture of papillary muscle)
- Trauma or surgery (mitral valvotomy)
- Infective endocarditis (due to perforation of mitral valve leaflet or chordae)
- Acute rheumatic fever (due to mitral valvulitis)
- Spontaneous rupture of chorda tendineae or myxomatous degeneration of valve.

Q. What are the **causes of pansystolic murmur**?

A. As follows:
- Mitral regurgitation
- Tricuspid regurgitation (TR)
- VSD.

Q. Is there any MDM in MR?

A. Yes, it may be present due to increased flow of blood through mitral valve (or if associated with MS).

Q. What are the signs of **severe MR**?

A. Severe MR is suggested by the following findings:
- Large left ventricle (apex is shifted, thrusting)
- Presence of third heart sound
- Presence of mid diastolic flow murmur (due to rapid filling of the left ventricle).

Q. What are the **complications** of MR?

A. As follows:
- Acute LVF
- Infective endocarditis
- Embolism
- Arrhythmia (atrial fibrillation, ectopics)
- CCF.

Q. Where the murmur **radiates** following the rupture of chorda tendineae?

A. As follows:
- Rupture of anterior leaflet of chorda tendineae—murmur radiates to axilla and back
- Rupture of posterior leaflet of chorda tendineae—murmur radiates to cardiac base and carotid arteries.

Q. How to **treat** MR?

A. As follows:

1. In mild to moderate case:
   - Diuretic
   - Vasodilator: ACE inhibitor
   - If fast AF: Digoxin
   - Anticoagulant if associated AF or history of pulmonary embolism
   - Prophylactic penicillin to prevent endocarditis

- Follow-up every 6 months by echocardiogram.
- If the ejection fraction falls to 55% and left ventricular dilatation >60 mm, valve replacement may be considered.

2. In severe MR or in progressively worsening MR—Replacement of valve.

Q. What type of **valve** should be replaced?

A. As follows:

- In young patient: Metallic valve
- In elderly patient: Tissue valve.

Q. What are the **indications** of surgery in MR?

A. As follows:

- Symptomatic.
- Asymptomatic patient with severe MR with mild to moderate LV dysfunction (EF 30 to 60% and end systolic dimension 45 to 55 mm).
- Asymptomatic patient with normal left ventricle and atrial fibrillation or pulmonary hypertension.

Q. What are the **types** of prosthetic valve?

A. Prosthetic valves are of 2 types:

1. Metallic valves:
- Starr-Edward valve (ball-cage valve)
- Bjork-Shiley valve (tilting disc)
- St Jude's valve (bi-leaflet, double tilting disc).

2. Tissue valves:
- Carpentier-Edwards valve
- Hancock porcine valve
- Ionescu Shiley valve (less used).

Note Tissue valve – 2 types:

- Xenograft: Made from porcine valve or bovine pericardium. These are less durable and may require replacement after 8 to 10 years. Anticoagulation is not required unless there is AF.
- Homograft: These are cadaveric valves (aortic or pulmonary human valve), particularly useful in young patient and in the replacement of infected valves.

Q. How to **detect** that the patient has prosthetic valves?

A. It is detected in the following ways:

- Usually there is a vertical mid-sternal scar mark of thoracotomy. (It may also be due to CABG).
- In metallic valve replacement, there is metallic sound on auscultation. However, modern mechanical valve (St Jude's valve) makes softer opening and closing sound than older valves.
- In case of tissue valve prosthesis, there is no metallic sound or plopping sound. Rather, there is a click.

Q. How to **detect clinically** whether the replaced valve is mitral or arotic?

A. As follows:

1. Mitral valve prosthesis is detected by:
- Site: Over the mitral valve
- Metallic sound is present, coincides with first heart sound (sharp closing)
- Normal second heart sound
- Diastolic flow murmur (MDM) may be present normally
- Sharp opening or closing sound or click that coincide with the carotid pulse.

2. Aortic valve prosthesis is detected by:

- Site: Over the aortic valve
- Metallic sound is present, coincides with second heart sound (sharp closing)
- Normal first heart sound. Ejection systolic flow murmur (ESM) may be present normally
- Sharp opening or closing sound or click that occurs shortly after the carotid pulse.

Note Remember the following:

Mostly, Starr-Edward valve is used.

Q. How to **detect**, if prosthetic valve is **leaking?**

A. As follows:

- In mitral valve prosthesis: Appearance of PSM indicates leaking (MDM may be normally present. Ball and cage valves project into the left ventricle and cause a low intensity ESM. Tissue valve and bileaflet valve can have a low intensity diastolic murmur. Consider any systolic murmur of loud intensity to be a sign of regurgitation and failure of the valve.).
- In aortic valve prosthesis: Appearance of EDM indicates leaking (ESM may be normally present as all types of valves produce a degree of outflow obstruction and thus have an ESM).

Q. What happens, if there is **dysfunction** of prosthetic valve?

A. Absence of opening and clicking or closing sounds indicates dysfunction. Unexplained heart failure may be due to dysfunction. Biological valve dysfunction is usually associated with regurgitant murmur.

Q. What are the **advantages and disadvantages** of different valves?

A. As follows:

1. In case of metallic valve:

- Advantage: Incidence of valve failure is less and more durable.
- Disadvantage: Incidence of thrombosis is usually high, requiring long-time anticoagulant therapy, even life long. There may be microangiopathic hemolytic anemia.

2. In case of tissue valve:

- Advantage: Incidence of thrombosis is less, hence long-time anticoagulant therapy is not required (short-term anticoagulant is used in postoperative period. Also, anticoagulant is required, if associated with AF). No hemolysis.
- Disadvantage: Incidence of valve failure is high due to stiffening and later tearing of valve leaflets over 10 years, and requires repeat valve replacement and is less durable. There is degeneration and calcification in advanced stage.

Q. What are the **complications** of metallic valve?

A. As follows:

- Thromboembolism
- Anticoagulation is needed which may lead to bleeding
- Microangiopathic hemolytic anemia
- Infective endocarditis.

Q. What are the **complications** of tissue valve?

A. As follows:

- Primary valve failure
- Perforation or rupture
- Degenerative changes

- Calcification
- Infective endocarditis.

Q. What are the **complications** of prosthetic valve?

A. As follows:

- Thromboembolism: More on metallic valve (common in mitral than aortic). Anticoagulant is necessary (INR should be between 3 and 4.5).
- Primary valve failure: Rare in metallic valve (common in tissue valve).
- Valve leaking.
- Dehiscence or detachment of valve from the site or valve ring resulting in paraprosthetic leak.
- Valve obstruction by thrombosis or calcification.
- Mechanical or microangiopathic hemolytic anemia (mainly in aortic valve in 10 to 20% in 10 years. Occurs due to metallic valve.).
- In tissue valve, there may be perforation, rupture, degenerative changes due to calcium deposition.
- Infective endocarditis, especially in dental procedure or catheterisation. Common organism is *Staphylococcus epidermidis*. Occasionally, treatment may be difficult, high mortality and may require to replace the valve again. If infection occurs within 60 days of valve replacement (early), it is mostly by contamination of intravenous (IV) cannula and if the infection occurs after 60 days (late), it is like other valve endocarditis.

Note Remember the following points:

- Ball and cage valve causes hemolysis more than other valve
- Tilting disc is more thrombogenic.

Q. How to **choose** a particular valve?

A. In the following way:

- In young patients, if no contraindication for anticoagulant therapy, metallic valve prosthesis is preferred.
- In elderly patient or if there is contraindication to anticoagulant therapy, tissue valve prosthesis is preferred.

Q. Which prosthesis is used in a **woman at child bearing age**?

A. Mechanical valves are now preferred for woman at child bearing age. During pregnancy, warfarin is substituted with IV unfractionated heparin in the first 6 to 12 weeks and last 2 weeks. This is associated with a low rate of warfarin embryopathy and of bleeding. However, subcutaneous heparin and low molecular weight heparin are not recommended at the present.

Recent studies have showed that women who need low doses of warfarin (5 mg or less) are at low risk for fetal warfarin embryopathy, bleeding, still birth or abortion. In these women, warfarin may be given throughout pregnancy but should be closely monitored.

Previously tissue valve was used for young woman considering the risk of anticoagulation at pregnancy. But with tissue valve, there is increased risk of early structural valve deterioration (SVD) during or shortly after the end of pregnancy. In addition, tissue valve is less durable and repeat valve replacement may be needed after about 10 years.

MIXED MITRAL STENOSIS WITH MITRAL REGURGITATION

The patient's history of present illness or presentation is same as in mitral stenosis.

GENERAL EXAMINATION

Mentions as in mitral stenosis or regurgitation (mentioned previously).

SYSTEMIC EXAMINATION

Cardiovascular system

- Pulse: 84/min, low in volume, normal rhythm and character
- JVP: Normal
- Blood pressure: 115/60 mm Hg.

Precordium

Inspection:

- Visible cardiac impulse in mitral area.

Palpation:

- Apex beat: In the left … intercostal space, … cm from midline, tapping in nature
- Thrill: Present in apical area, both systolic and diastolic.

Auscultation:

- First heart sound: Louder in all the areas
- Second heart sound: Normal in all the areas
- There is a mid-diastolic murmur in mitral area and also a pansystolic murmur in mitral area, which radiates to the left axilla.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Present the history and physical findings as mentioned above.

My diagnosis is: Chronic rheumatic heart disease with mitral stenosis with mitral regurgitation.

Q. What is the **predominant** lesion and why?

A. Predominant lesion is MS, because:

- Pulse: Low volume
- Apex beat: Not shifted and tapping in nature
- First heart sound is loud.

Q. What are the findings if **MR is predominant**?

A. If MR is predominant:

- Pulse: Normal/high volume
- Apex beat: Shifted and thrusting in nature

- First heart sound is soft or absent
- There may be third heart sound.

Q. What **investigations** should be done?

A. As follows:

- X-ray chest
- ECG
- Echocardiography, preferably color Doppler.

Q. What is the **cause** of mixed MS and MR?

A. Chronic rheumatic heart disease.

Q. In which lesion of MR or MS, **endocarditis** is common?

A. Endocarditis is common in MR.

Q. How will you **treat** your case?

A. As follows

- Conservative treatment: Rest, diuretic, prophylactic penicillin to prevent infective endocarditis, antiplatelet like aspirin, warfarin to prevent thromboembolism.
- In severe case: Valve replacement may be needed.

AORTIC STENOSIS

CHIEF COMPLAINTS

- Shortness of breath for … months
- Palpitation for … months
- Chest pain for … months
- Loss of consciousness ... hours.

HISTORY

History of present illness: The patient states that he was quite well … months back. Since then, he has been suffering from shortness of breath, which is more marked on moderate to severe exertion and relieved by rest. This is not associated with cough. Occasionally, he experiences nocturnal breathlessness, usually at late hours of night, which compels him to get up from sleep, walk and take deep breath to be comfortable. There is no history of breathlessness on lying flat (orthopnea).

The patient also complains of occasional palpitation and chest pain, which occur during mild to moderate exertion. The pain does not radiate and it is relieved by taking rest. The patient also experiences occasional dizziness. There are 2 episodes of loss of consciousness in the last 3 months, each episode lasted for few minutes. It was preceded by giddiness and lightheadedness, but no convulsion or urinary or fecal incontinence or tongue biting.

History of past illness: He was always in good health. There is no history of rheumatic fever or other illnesses.

Family history: All the members are in good health. No history of such illnesses in the family.

Personal history: He is a school teacher. He smokes 2 to 3 cigarettes per day for the last 5 years.

Socioeconomic history: He comes from a lower middle-class family, living in a tin shed house in a rural area with access to sanitary toilet and arsenic free tubewell water. His monthly income is about 4000 TK.

Drug history: Nothing significant.

Psychiatric history: There is no history of any psychiatric illness.

GENERAL EXAMINATION

As in other valvular diseases written above, mention as your findings.

SYSTEMIC EXAMINATION

Cardiovascular System

- Pulse: 92/min, low volume and slow rising, normal in rhythm, no radiofemoral or radioradial delay.
- JVP: Normal.
- BP: 95/80 mm Hg (low systolic, normal diastolic and narrow pulse pressure).

Note

However, slow rising pulse and low pulse pressure may not be found in elderly, due to the stiffening of the arteries.

Precordium

Inspection:

- Visible cardiac impulse in mitral area (or nothing).

Palpation:

- Apex beat—In the left … intercostal space, ... cm from midline, heaving in nature
- Systolic thrill—Present in aortic area.

Auscultation:

- First heart sound—Normal in all the areas.
- Second heart sound—A_2 is soft in all the areas, P_2 is normal (may be reversed splitting of 2nd heart sound).
- Fourth heart sound may be present (due to atrial contraction).
- There is a harsh ejection systolic murmur in aortic area, which radiates towards the neck.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, a 40-year-old school teacher, smoker, nondiabetic, non-hypertensive, presented with shortness of breath for … months, which is more marked on moderate to severe exertion and relieved by rest. This is not associated with cough, wheeze or hemoptysis. He occasionally complains of paroxysmal nocturnal dyspnea but no orthopnea. The patient also complains of occasional palpitation and chest pain, which occur during mild to moderate exertion. There is no radiation of pain and it is relieved by taking rest. The patient also experiences occasional dizziness. There are 2 episodes of loss of consciousness in the last 3 months; each episode lasted for few minutes. It was preceded by giddiness and lightheadedness, but no convulsion or urinary or fecal incontinence or tongue biting. There is no history of rheumatic fever or other illness. Other history does not reveal anything significant. No family history of such illness. He used to take diuretics, vitamins prescribed by the local physicians.

On examination, general examination: Nothing significant.

Examination of cardiovascular system: Mention as above.

Other systems revealed no abnormalities.

My diagnosis is aortic stenosis.

Q. Why is your diagnosis aortic stenosis?

A. Because:

- In the history, there is exertional dyspnea, chest pain and syncopal attack.
- On examination, there is systolic thrill in aortic area, soft aortic component of second sound (A_2) and ejection systolic murmur in aortic area that radiates to the carotid.

Q. What are your differential diagnoses?

A. As follows:

- Pulmonary stenosis
- Hypertrophic cardiomyopathy (HCM).

Q. Why not pulmonary stenosis?

A. In pulmonary stenosis, findings are:

- Systolic thrill in pulmonary area.
- Left parasternal lift and epigastric pulsation may be present (due to RVH).
- P_2 is soft, A_2 is normal (wide splitting of the second heart sound may be present).
- Ejection systolic murmur in pulmonary area, which radiates to the left side of neck (murmur is more on inspiration).
- Apex is normal (not heaving as in AS).

Q. Why not HCM?

A. In HCM, the findings are:

- Pulse is jerky.
- Prominent **"a"** wave in JVP.
- Double impulse at the apex (palpable 4th heart sound due to left atrial hypertrophy).
- Systolic thrill in left lower parasternal area.
- Associated pansystolic murmur due to MR.
- Family history of HCM may be present or there may be history of sudden death in family.

Note Remember the following:

In HCM, echocardiography is very helpful for diagnosis. ECG shows LVH and bizarre abnormalities like pseudoinfarction pattern, deep T inversion.

Q. What investigations do you suggest in AS?

A. As follows:

- X-ray chest (may be normal in early case. Enlarged left ventricle and dilated ascending aorta, calcification of valve on lateral view).
- ECG (LVH, may be LBBB, complete AV block due to calcification of ring may be found).
- Echocardiogram, preferably color Doppler echocardiography.
- Cardiac catheterization (mainly to identify associated coronary artery disease. Also to measure the gradient between left ventricle and aorta).

RELATED QUESTIONS AND ANSWERS

Q. Does the loudness of the murmur indicate severity?

A. No, prolongation of murmur indicates severity. Loudness of murmur may be associated with mild stenosis.

Q. What are the causes of aortic stenosis?

A. As follows:

- Chronic rheumatic heart disease
- Bicuspid aortic valve (common in male)
- Calcification in old age
- Congenital (in early age).

Causes of aortic stenosis according to age:

- **Infants, children, adolescents:**
  - Congenital aortic stenosis
  - Congenital subvalvular aortic stenosis
  - Congenital supravalvular aortic stenosis.
- **Young adults to middle-aged:**
  - Calcification and fibrosis of congenitally bicuspid aortic valve
  - Rheumatic aortic stenosis.
- **Middle-aged to elderly:**
  - Senile degenerative aortic stenosis
  - Calcification of bicuspid valve
  - Rheumatic aortic stenosis.

Remember the following points in elderly patient:

- Aortic stenosis (AS) is the most common form of valve disease in old age
- It is a common cause of syncope, angina and heart failure in this age group
- Low pulse pressure and slow rising pulse may not be present due to stiffening of the arteries
- Surgery can be successful in the absence of co-morbidity but operative mortality is higher. Prognosis is poor in symptomatic patients without surgery
- Biological valve is more preferable than mechanical valves. Anticoagulant is not needed.

Q. What is the role of **ETT** in AS?

A. ETT should be avoided in symptomatic patient with aortic stenosis as it may be fatal. However, it may be done in asymptomatic cases with high grade aortic stenosis. May be helpful in deciding the role of surgery.

Q. What are the **types** of aortic stenosis?

A. Three types:

- Valvular: Involving valve cusps. It is the most common type.
- Subvalvular: Narrowing of outflow tract of left ventricle.
- Rarely supravalvular: Constriction at the first part of aorta.

Q. What is the **type of pulse** in AS?

A. Plateau pulse, it is a slow rising, small volume pulse (pulsus parvus). It may be late peaking (pulsus tardus).

Q. What is aortic sclerosis? How to **differentiate** from aortic stenosis?

A. It is a degenerative condition in which there is thickening of aortic valve cusps, common in elderly. It does not produce any significant obstruction to the outflow of blood.

Features	Aortic stenosis	Aortic sclerosis
1. Pulse volume	Low volume, slow rising	Normal
2. Apex beat	Heaving	Normal
3. Thrill	Systolic	No thrill
4. A_2	Absent or soft	Normal
5. ESM and radiation	Present, radiates to the neck	Present, usually no radiation

Note Risk of aortic sclerosis:

- There may be calcification leading to AS. There are some risk factor like hyperlipidemia, diabetes mellitus, smoking, hypertension are prone to develop aortic calcification.

Q. What are the **presentations** of aortic stenosis?

A. As follows:

- Breathlessness, mainly on exertion
- Palpitation
- Anginal pain (in 50% cases with or without coronary artery disease)
- Syncope: Specially during effort (which may be due to inadequate cardiac output or reflex vasodilatation after exercise or arrhythmia), causing cerebral hypoperfusion
- Sudden death (probably due to ventricular fibrillation).

Note Remember the following points:

- Aortic stenosis may be asymptomatic if it is mild or congenital, even may be asymptomatic throughout life.
- In elderly—May be associated with complete heart block or LBBB.

Q. **Why** anginal pain occurs in AS?

A. There is left ventricular hypertrophy, so there is more oxygen demand. Also, there is reduced coronary flow due to less cardiac output (limitation of duration of diastole).

Q. What are the **signs of severe** AS?

A. Signs of severe AS are:

- Pulse is feeble or absent. Slow rising plateau pulse may be present.
- Systolic aortic thrill.
- Absent or soft A_2 (or single S_2).
- Harsh, loud, prolonged murmur with late peaking (soft and short ESM with early peaking suggest mild stenosis).
- Reversed splitting of second heart sound.
- Presence of fourth heart sound.
- Presence of heart failure or LVF (late sign).

Note Also remember the following points:

- Normal area of aortic valve is 1.5 to 2 cm^2. It is severe, if the area is < 1 cm^2 or valve mean pressure gradient is > 50 mm Hg.
- Critical aortic stenosis: If the valve area is < 0.7 cm^2 or valve pressure gradient is > 70 mm Hg.

Q. What are the **complications** of aortic stenosis?

A. As follows:

- Left ventricular failure
- Infective endocarditis (10% cases)
- Sudden death due to ventricular fibrillation
- Complete heart block (in case of calcification of aortic valve)
- Systemic embolism.

Q. What is the **prognosis** of AS in symptomatic patients?

A. If aortic valve is not replaced, the onset of angina, syncope and dyspnea has been shown to correlate with an average time to death of 5, 3 and 2 years.

Q. How to **treat** aortic stenosis?

A. As follows:

- In mild or asymptomatic cases and if valvular pressure gradient < 50 mm Hg—follow-up (periodic echocardiogram should be done). Conservative symptomatic management is given.
- If symptomatic or even single syncopal attack immediate valve replacement.
- In asymptomatic patient with severe AS and a deteriorating ECG—valve replacement is also recommended.
- If the patient is unfit for surgery, percutaneous valvuloplasty may be attempted.
- Aortic balloon valvuloplasty is useful in congenital AS. But this is of no value in old age with calcific AS (valve replacement is necessary in such cases).
- In children, elderly or pregnancy—valvotomy may be done.
- Anticoagulant is only necessary if there is associated atrial fibrillation or mechanical valve prosthesis is used.

Q. Which prosthetic valve is **preferred** in elderly patient?

A. Usually biological or tissue valve is preferred than mechanical one, as biological valve does not require anticoagulation. In younger age, mechanical valve is preferred, but anticoagulant should be given.

Q. What are the **indications of surgery**?

A. As follows:

- All symptomatic patient (such as syncope).
- If mean systolic pressure gradient is > 50 mm Hg (left ventricular systolic pressure > aorta).
- If the valve area is < 0.7 cm^2 (normal – 2.5 to 3 cm^2).
- Asymptomatic patient undergoing surgery for coronary disease, other valve, LV dysfunction, progressive decline in LVEF, marked LVH.
- Abnormal BP in response to exercise.
- VT.

Q. If the patient with AS has **bleeding** per rectum, what is the likely underlying cause?

A. Angiodysplasia of the colon (Heydis syndrome).

AORTIC REGURGITATION

CHIEF COMPLAINTS

- Palpitation for … months
- Shortness of breath for … months
- Occasional cough for … months.

HISTORY

History of present illness: The patient states that he was alright … months back. Since then, he has been suffering from occasional palpitation and shortness of breath, which usually occurs during mild to moderate exertion, relieved by taking rest. There is no history of orthopnea or paroxysmal nocturnal dyspnea. There is no diurnal variation or association with dust, fume or cold exposure. The patient also complaints of occasional dry cough, but there is no chest pain or hemoptysis. Sometimes he experiences dizziness, but no loss of consciousness.

History of past illness

Family history

Personal history

Socioeconomic history

Drug history: Mention according to the statement of the patient.

GENERAL EXAMINATION

As in other valvular diseases written before.

SYSTEMIC EXAMINATION

Cardiovascular System

- Pulse: 92/min, regular, high volume, collapsing type
- JVP: Normal
- There is dancing carotid pulse in the neck (Corrigan's sign)
- BP: 160/30 mm Hg (high systolic, low diastolic and wide pulse pressure).

Precordium

Inspection:

- Visible cardiac impulse.

Palpation:

- Apex beat: Shifted in left … intercostal space, ... cm from midline, thrusting in nature
- Thrill: Present in left parasternal area, diastolic in nature.

Auscultation:

- First heart sound: Normal in all the areas
- Second heart sound: A_2 is absent and P_2 is normal

- There is an early diastolic murmur, which is high pitched, blowing, best heard in the left lower parasternal area, with patient bending forward and breathing hold after expiration.

Note Mention if the following findings are present:

- Ejection systolic murmur (in aortic area which radiates to the neck, due to increased stroke volume and flow through the aortic valve).
- A soft mid-diastolic murmur (called Austin Flint murmur).
- Duroziez's murmur (over the femoral artery).
- Capillary pulsation (seen in the nail bed, inner side of lip, fundus during ophthalmoscopy).

Examination of other systems reveals no abnormalities.

SALIENT FEATURE

Mr …, 30-year-old, businessman, normotensive, nondiabetic, smoker, presented with occasional palpitation and shortness of breath for … months, which usually occurs during mild to moderate exertion and relieves after taking rest. There is no history of orthopnea or paroxysmal nocturnal dyspnea. There is no diurnal variation or association with dust, fume or cold exposure. The patient also complaints of occasional dry cough, but there is no chest pain or hemoptysis. Sometimes he experiences dizziness, but no loss of consciousness. There is no family history of such illness. He took some diuretics prescribed by local physicians.

General examination: Mention as above.

Examination of cardiovascular system: Mention as above.

Examination of other systems reveals no abnormalities.

My diagnosis is aortic regurgitation.

Q. Why your diagnosis is AR?

A. Because:

- Pulse is high volume and collapsing
- Dancing carotid pulse
- High systolic and low diastolic BP (wide pulse pressure)
- Presence of EDM in the left lower parasternal area.

Q. What is your differential diagnosis?

A. Pulmonary regurgitation (PR).

Q. How to differentiate AR from PR?

A. In PR, findings are:

- Early diastolic murmur in pulmonary area (called Graham Steel murmur), which is more prominent on inspiration.
- Evidence of pulmonary hypertension may be present (e.g. palpable P_2, left parasternal heave, epigastric pulsation, etc.).

Note

Pulmonary regurgitation is rare as an isolated phenomenon, usually associated with pulmonary artery dilatation due to pulmonary hypertension, secondary to other diseases (e.g. mitral stenosis).

Q. Mention **one investigation** to confirm your diagnosis.

A. Echocardiography, preferably color Doppler.

Q. What **investigations** do you suggest in this case?

A. As follows:

- X-ray chest (cardiomegaly, dilated ascending aorta, pulmonary edema)
- ECG (LVH)
- Echocardiogram, preferably color Doppler
- Cardiac catheterization
- Other investigations to find out the cause according to the clinical suspicion.

RELATED QUESTIONS AND ANSWERS

Q. Why this is called **water hammer pulse**?

A. The name originated from a Victorian toy, consisted of a sealed tube, half filled with water and half being vacuum. Inversion of the tube causes the fluid to fall rapidly without air resistance and strike the end like hammer blow.

Q. Are "high volume pulse" and "collapsing pulse" synonymous?

A. Collapsing pulse is always high volume, but all high volume pulse are not collapsing.

Q. What are the causes of **high volume pulse**?

A. As follows:

- Aortic regurgitation
- Hypertension
- Hyperdynamic circulation due to any cause (severe anemia, thyrotoxicosis, arteriovenous fistula, fever, etc.)
- PDA.

Q. What is **collapsing pulse**? What are the **causes**?

A. In collapsing pulse, there is rapid upstroke and descent of pulse, seen by raising the arm above the head. Causes are:

- AR (the most common cause)
- Hyperdynamic circulation due to any cause (see above)
- PDA
- Rupture of sinus of Valsalva
- Large arteriovenous communication.

Q. In AR, what other **signs** do you want to look for?

A. As follows:

- Quinke's sign: Capillary pulsation at the nail bed (alternate flushing and paleness of skin at the root of the nail while pressure is applied at the tip of the nail). It may be normally present and better seen with glass slide.
- de Musset's sign: Head nodding with heart beat (with each pulse).
- Duroziez's sign: Usually diastolic (may be systolic) murmur over the femoral artery on gradual compression of the vessel and ausculted proximally.
- Pistol shot: May be heard over femoral artery (Traube's sign).
- Hill's sign: High BP in legs than arms (high systolic BP, 60 mm difference) indicates severe AR.
- Mueller's sign: Pulsation in uvula with heart beat.

Note

Most of the signs are rare and unhelpful.

Q. What will you see **in the eye and mouth** in a patient with AR?

A. As follows:

- Eye: Argyll Robertson pupil (may be present in neurosyphilis), dislocated lens, irregular pupils, iridodonesis (found in Marfan's syndrome).
- Mouth: High arched palate (Marfan's syndrome).

Note

Also look for evidence of ankylosing spondylitis, rheumatoid arthritis which may cause aortic regurgitation.

Note To diagnose AR, remember the formula of 3:

- 3 pulse: Collapsing (water hammer), dancing carotid and capillary pulsation.
- 3 BP: Rise of systolic, fall of diastolic and wide pulse pressure.
- 3 murmur: Early diastolic murmur, Austin Flint murmur and ejection systolic murmur.

Q. What are the causes of **wide pulse pressure**?

A. As follows:

- AR
- PDA
- A-V fistula
- Hyperdynamic circulation (thyrotoxicosis, anemia, beriberi, pregnancy).

Q. What are the causes of **EDM**?

A. As follows:

- Aortic regurgitation
- Pulmonary regurgitation (evidence of pulmonary hypertension is present and other peripheral signs of AR are absent).

Q. Why there is **ESM** in AR?

A. Due to increased flow through aortic valve without aortic stenosis (or may be associated with AS).

Q. Why there is MDM in AR **(Austin Flint murmur)**?

A. It is due to regurgitant flow from aortic valve causing vibration of the anterior leaflet of mitral valve.

Q. Why not this **MDM** is due to mitral stenosis?

A. In MS, there should be:

- Tapping apex beat
- Loud first heart sound
- MDM associated with presystolic accentuation
- Opening snap.

Q. What are the signs of **severe AR**?

A. Signs of severe AR:

- Prolonged EDM
- A_2 absent
- Presence of left ventricular 3rd heart sound
- Presence of Austin Flint murmur
- Signs of LVF
- Signs of enlarging heart.

Q. What are the **causes of AR**?

A. As follows:

- Chronic rheumatic heart disease
- Infective endocarditis
- Syphilitic aortitis
- Bicuspid aortic valve
- Dissecting aneurysm affecting ascending aorta
- Hypertension (by aortic dilatation)
- Marfan's syndrome
- Seronegative arthritis (ankylosing spondylitis, Reiter's syndrome)
- Rheumatoid arthritis
- Cystic medial necrosis
- Congenital.

Causes of AR according to the site or abnormality:

- Due to involvement of valve:
  - Rheumatic fever
  - Infective endocarditis
  - Bicuspid aortic valve
  - Trauma
- Aortic root dilatation:
  - Marfan's syndrome
  - Dissecting aneurysm affecting ascending aorta
  - Syphilitic aortitis
  - Hypertension
  - Trauma
  - Seronegative arthritides (ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy)
  - SLE
  - Rheumatoid arthritis
  - Pseudoxanthoma elasticum
  - Osteogenesis imperfecta
  - Rare causes—appetite suppressants (like fenfluramine, phentermine).

Q. What are the **causes of acute AR**?

A. As follows:

- Acute bacterial endocarditis
- Acute rheumatic fever (due to valvulitis)
- Dissecting aneurysm affecting ascending aorta
- Trauma.

Note

In acute AR, there is soft, short, early diastolic murmur with diastolic thrill. Most patients have heart failure. Peripheral signs and cardiomegaly are absent. It should be treated by emergency surgery.

Q. What are the **complications** of AR?

A. As follows:

- Acute LVF
- Infective endocarditis
- Arrhythmia.

Q. How to **differentiate** AR of rheumatic origin and due to other causes?

A. In rheumatic origin:

- History of rheumatic fever
- Other valvular lesion: Commonly mitral
- Echocardiogram: There is thickening and shortening of cusps, fusion of commissures (If AR is due to other cause: There is dilatation of aorta or valve ring).

Q. How to **differentiate** syphilitic AR and rheumatic AR?

A. As follows:

Features	Syphilitic AR	Rheumatic AR
1. Age	>40 years	Early age
2. History of	Syphilis	Rheumatic fever
3. EDM	In aortic area (right sternal border)	In left lower parasternal area
4. Peripheral signs	Usually absent	Present
5. Lesion	Only AR, never AS	Both may be present
6. Echocardiogram	No cusp involvement	Cusp involvement
7. Aorta	Dilated, calcification may occur	No calcification

Note

Syphilis never causes AS, only AR.

Q. How to **treat** AR?

A. As follows:

1. In asymptomatic moderate to severe AR with normal LV function—long acting nifedipine.
2. In symptomatic patient with:
   - Normal LV function: Long acting nifedipine
   - LV dysfunction: Digitalis, ACE inhibitor, diuretic
   - Heart failure: Digitalis, ACE inhibitor, diuretic.
3. In severe case: Valve replacement.

Indications of surgery:

1. Symptomatic patient.
2. Asymptomatic patient with
   - LV systolic dysfunction (EF < 50%)
   - LV dilatation (LV end systolic dimension >55 mm or LV end diastolic dimension >75 mm).
   - Aortic root dilatation >50 mm.

Note

The valve should be replaced before significant left ventricular dysfunction occurs.

Q. What are the **causes** of angina in AR?

A. As follows:

- Low diastolic blood pressure compromise the coronary perfusion pressure causing angina.
- Marked LVH.

MIXED AORTIC STENOSIS AND REGURGITATION

CHIEF COMPLAINTS

- Breathlessness on exertion for … months
- Palpitation for … months
- Chest pain for … months
- Occasional dizziness for … months.

HISTORY

History of present illness: The patient states that he had been well … months back. For the last … months, he has been suffering from shortness of breath and palpitation on moderate to severe exertion. Sometimes, he experiences orthopnea and paroxysmal nocturnal dyspnea. His breathlessness is not related to dust, fume or change in weather. There is no diurnal variation.

The patient also complains of central chest pain, which is aggravated during moderate exertion and is relieved by taking rest. The pain is compressive in nature, without any radiation. Occasionally he feels dizzy. He became unconscious twice during the last … months. Each episode was preceded by giddiness and lightheadedness and persisted for few minutes. There is no history of cough, fever or swelling. His bowel and bladder habits are normal.

History of past illness

Personal history

Family history

Socioeconomic history

Drug history: Mention according to the statement of the patient.

GENERAL EXAMINATION

Mention as described in other cases, according to your finding.

SYSTEMIC EXAMINATION

Cardiovascular System

- Pulse: 98/min, low volume and slow rising, normal in rhythm, pulsus bisferiens is present (in carotid).
- JVP: Normal.
- BP: Low systolic and normal diastolic, narrow pulse pressure.

Precordium

Inspection:

- Visible cardiac impulse.

Palpation:

- Apex beat: Shifted in left … intercostal space, … cm from midline, heaving in nature.
- Systolic thrill: Present in aortic area.

Auscultation:

- First heart sound: Normal in all the areas.
- Second heart sound: A_2 is soft or absent and P_2 is normal.
- There is an ejection systolic murmur in aortic area which radiates to the neck and also there is an early diastolic murmur in the left lower parasternal area.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr…., 40-year-old, businessman, normotensive, nondiabetic, smoker, presented with shortness of breath and palpitation on moderate to severe exertion for … months. Sometimes he experiences orthopnea and paroxysmal nocturnal dyspnea. His breathlessness is not related to dust, fume or change in weather. There is no diurnal variation. The patient also complains of central chest pain, which is aggravated during moderate exertion and is relieved by taking rest. The pain is compressive in nature, without any radiation. Occasionally he feels dizzy. He became unconscious twice during the last … months. Each episode was preceded by giddiness and lightheadedness and persisted for few minutes. There is no history of cough, fever or swelling. His bowel and bladder habits are normal. He took some diuretics the name of which he cannot mention. There is no such illness in his family.

On examination, general examination—mention as above.

Examination of cardiovascular system—mention as above.

Examination of other systems reveals no abnormalities.

My diagnosis is aortic stenosis with aortic regurgitation.

Q. What is your **differential** diagnosis?

A. There is combined systolic and diastolic murmur. So this may be confused with conditions that present with continuous murmur like:

- Patent ductus arteriosus (murmur is called machinery murmur or train in a tunnel)
- Pulmonary arteriovenous fistula
- Pulmonary stenosis with pulmonary regurgitation.

Q. Could it be **purely AR** without stenosis?

A. Yes, ESM here may be due to increased flow through aortic valve without AS.

Q. What do you think the likely **cause** in this case?

A. Chronic rheumatic heart disease.

Q. Could it be due to **syphilis**?

A. No, **syphilis never causes AS.**

Q. What is the **predominant** lesion in this case and why?

A. Predominant lesion is aortic stenosis, because:

- Pulse: Low volume and slow rising.
- Blood pressure: Low systolic and normal diastolic, narrow pulse pressure.
- Apex beat is heaving.
- Systolic thrill in aortic area.
- A_2: Absent.

Note

If AS is predominant, there may be history of more anginal pain and syncopal attack.

Q. What are the findings, if **AR** is predominant?

A. If AR is predominant, there will be:

- Pulse: High volume and collapsing (water hammer type).
- Apex beat: Shifted and thrusting.
- Blood pressure: Increased systolic, fall of diastolic and wide pulse pressure.

Note

If AR is predominant, in history, palpitation will be more and there will be less anginal pain and syncopal attack.

RELATED QUESTIONS AND ANSWERS

Q. What **investigations** do you suggest?

A. As follows:

- X-ray chest
- ECG (LVH)
- Echocardiogram, preferably color Doppler
- Cardiac catheterization.

Q. How to **treat** the case?

A. As follows:

- In mild to moderate case: Follow-up.
- In severe case: Valve replacement.

CONGESTIVE CARDIAC FAILURE WITH VALVULAR LESION

CHIEF COMPLAINTS

- Breathlessness on exertion for … months
- Cough with mucoid expectoration for … months
- Palpitation for … months
- Pain in right upper abdomen for … months
- Swelling of legs for … months
- Weight loss, anorexia, weakness for … months.

HISTORY

History of present illness: According to the patient's statement, she was relatively alright … months back. Since then, she has been suffering from progressively increasing difficulty in breathing. Initially she felt breathless on moderate to severe exertion, but now it is more marked even during normal activities like going to the toilet or dressing. She also complains of cough, with expectoration of mucoid sputum, but with no hemoptysis or wheeze. The cough is not aggravated by exposure to cold, dust, fume, etc. Occasionally, she experiences nocturnal breathlessness, at late hours of night, for which she has to get up from sleep and walk to take deep breath, which makes her comfortable. There is no history of breathlessness on lying flat (orthopnea).

The patient also experiences occasional palpitation, aggravated on mild exertion and relieved by taking rest. She also noticed pain in the right upper abdomen, which aggravates on lying on right lateral position. The pain is dull aching in nature, but no radiation to any site. She also complains of gradual swelling of both legs, which is more marked during prolonged sitting or standing. The swelling used to disappear while she gets up from sleep early in the morning. She also complains of weakness, loss of appetite and loss of about one third of her body weight within the last … months.

History of past illness: There is no history of rheumatic fever or any cardiac disease. She does not give any history suggestive of COPD (to exclude cor pulmonale). There is no history of hypertension, diabetes mellitus.

Family history

Personal history

Socioeconomic history

Drug history: Mention according to the statement of the patient.

GENERAL EXAMINATION

- Appearance: Ill looking and dyspneic
- Decubitus: Propped up
- Built: Emaciated
- Nutritional status: Below average
- Anemia: Moderately anemic
- Cyanosis: Present
- Edema: Present, pitting

- No jaundice, clubbing, koilonychia, leukonychia or lymphadenopathy or thyromegaly
- Pulse: 104/min, low volume and regular in rhythm
- Blood pressure: 100/70 mm Hg
- Temperature: 97.6ºF
- Respiratory rate: 30/min.

SYSTEMIC EXAMINATION

Cardiovascular System

- Pulse: 104/min, low volume, regular in rhythm, normal in character, no radio-radial or radio-femoral delay and the condition of the vessel wall is normal. All the peripheral pulses are normal.
- Blood pressure: 100/70 mm Hg.
- JVP: Engorged … cm and pulsatile.

Precordium

Inspection:

- There is visible cardiac impulse in apical area and also visible epigastric pulsation.

Palpation:

- Apex beat is in left … intercostal space, 9 cm from midsternal line, normal in character
- Thrill: Absent
- P_2 is palpable in pulmonary area
- Left parasternal heave and epigastric pulsation are present
- (Mention other findings of vulvular lesion, if present).

Auscultation:

- Mention the heart sounds according to the vulvular lesion (all the heart sounds may be soft).
- Murmur: Mention which one is present.

Abdomen

Inspection:

- Mention according to your findings (may be all normal).

Palpation:

- Liver is enlarged … cm, from the right costal margin in mid clavicular line. It is tender, soft in consistency, margin is sharp, surface is smooth. Upper border of the liver dullness is in right 4th intercostal space in midclavicular line, no hepatic bruit or rub.
- Other findings: Mention accordingly.

Respiratory System

- May show signs of emphysema or chronic bronchitis (to exclude cor pulmonale).

Other systemic examinations reveals no abnormalities.

SALIENT FEATURE

The patient Mrs …, 38-year-old, housewife, normotensive, nondiabetic, nonsmoker, presented with progressively increasing difficulty in breathing for … months. Initially she felt breathless on moderate to severe exertion, but now it is more marked even during normal activities like going to toilet or dressing. She also complains of cough, with expectoration of mucoid sputum, but with no hemoptysis or wheeze. The cough is not aggravated by exposure to cold, dust, fume, etc. Occasionally, she experiences nocturnal breathlessness, at late hours of night, for which she has to get up from sleep and walk to take deep breath, which makes her comfortable. There is no history of breathlessness on lying flat (orthopnea).

The patient also experiences occasional palpitation, aggravated on mild exertion and relieved by taking rest. She also noticed pain in the right upper abdomen, which aggravates on lying on right lateral position. The pain is dull aching in nature, but no radiation to any site. She also complains of gradual swelling of both legs, which is more marked during prolonged sitting or standing. The swelling used to disappear while she gets up from sleep early in the morning. She also complains of weakness, loss of appetite and loss of about one third of her body weight within the last … months. There is no history of rheumatic fever or any cardiac disease. She does not give any history suggestive of COPD. There is no history of hypertension, diabetes mellitus. There is no family history of such illness. She used to take tablet frusemide and inhaler salbutamol as prescribed by local physicians.

On examination, general examination—mention as above.

Examination of cardiovascular system and abdomen—mention as above.

Other systems reveal no abnormalities.

My diagnosis is congestive cardiac failure (with … vulvular lesion – mention according to your finding).

Q. Why is it CCF?

A. Because there is engorged and pulsatile neck veins, enlarged tender liver and dependent pitting edema.

Q. What are your **differential diagnoses?**

A. As follows:

- Chronic cor pulmonale
- Nephrotic syndrome
- Cirrhosis of liver.

Q. What is **cor pulmonale**?

A. It is defined as right ventricular hypertrophy with or without failure, secondary to the diseases of lung parenchyma, pulmonary vessels or thoracic bony abnormality.

Q. Why is this **not a case of cor pulmonale**?

A. This is not a case of cor pulmonale, because there is no previous history of lung disease like chronic bronchitis, emphysema (COPD) or ankylosing spondolytis. Also on examination, there is no finding in chest such as kyphosis, scoliosis, barrel shaped chest or no findings in the lung suggestive of COPD.

Also, if any vulvular lesion is present (e.g. MS or MR), mention it, which is against cor pulmonale.

Q. Why not nephrotic syndrome?

A. In nephrotic syndrome, the face is swollen first, followed by abdomen and legs and ultimately generalized edema. Here facial swelling is absent. Also the engorged pulsatile neck vein and tender hepatomegaly are against NS.

Q. Why not **cirrhosis** of liver?

A. Because there are no stigmata of CLD.

Q. What **investigations** do you suggest in this case?

A. As follows:

- X-ray chest (cardiomegaly, plethoric lung fields)
- ECG
- Echocardiogram
- Others: CBC, ESR, urea, creatinine, electrolytes, serum total protein and AG ratio, lung function test (if COPD)
- BNP, ANP.

RELATED QUESTIONS AND ANSWERS

Q. What is **heart failure**?

A. It is defined as failure of the heart to maintain adequate cardiac output to meet the demand of the tissue or can do so only at the expense of an elevated filling pressure.

Q. What are the **cardinal signs** of congestive cardiac failure?

A. It actually means right heart failure. Cardinal signs of CCF are:

- Engorged and pulsatile neck veins
- Enlarged and tender liver
- Dependent pitting edema.

Note CCF may be associated with:

- Pleural effusion (commonly right sided, may be bilateral)
- Ascites
- Jaundice due to hepatic congestion (or cirrhosis, called cardiac cirrhosis).

Q. What are the **causes** of CCF?

A. As follows:

- Secondary to left sided heart failure (common cause)
- Mitral stenosis with pulmonary hypertension
- Chronic cor pulmonale due to any cause
- Pulmonary hypertension
- Pulmonary valve disease (stenosis or regurgitation)
- Tricuspid regurgitation
- Shunt anomaly (ASD, VSD), when there is reversal of shunt (Eisenmenger's syndrome)
- Cardiomyopathy
- Right ventricular myocardial infarction.

Q. What is **BNP**?

A. **B-type natriuretic peptide (BNP)** is a 32 amino acid polypeptide secreted by the left ventricle of the heart in response to excessive stretching of heart muscle cells. It is elevated in left ventricular systolic dysfunction. It may aid in the diagnosis and assess the prognosis and response to therapy in patient with heart failure. It helps to differentiate heart failure from other conditions (like bronchial asthma) that might mimic heart failure. However, BNP level may be elevated in renal failure (due to low clearance), pulmonary embolism, pulmonary hypertension, atrial fibrillation, acute myocardial

infarction, chronic hypoxia and sepsis. Originally, BNP was isolated from porcine brain and was called brain natriuretic peptide.

Q. What is the **functional classification** of cardiovascular disease status?

A. A close relationship of symptoms and exercise is the hallmark of heart disease. New York Heart Association (NYHA) functional classification of cardiovascular status is as follows:

- **Grade I:** No limitation during ordinary activity (asymptomatic).
- **Grade II:** Slight limitation during ordinary activity (symptomatic with mild activity).
- **Grade III:** Marked limitation of normal activities without symptoms at rest (symptomatic with moderate activity).
- **Grade IV:** Unable to undertake physical activity without symptoms. Symptoms may be present at rest (symptomatic at rest).

Q. How to **treat** CCF?

A. As follows:

- Complete rest.
- Restriction of fluid and salt.
- Diuretic (frusemide or bumetanide).
- Aldosterone receptor antagonist (e.g. spironolactone, eplerenone).
- Vasodilator (ACE inhibitor or ARB).
- β-blocker (especially bisoprolol 1.25 mg daily and gradually increased over 12 weeks up to 10 mg daily) may be used. It reduces the risk of arrhythmia and sudden death. β-blocker should not be initiated at a high dose since it may precipitate acute on chronic heart failure. But when given in a small incremental dose (as above), it can increase ejection fraction, improve symptoms, reduce frequency of hospitalization and reduce mortality in patient with chronic heart failure.
- Digoxin (helpful in CCF with atrial fibrillation).
- Treatment of arrhythmia (amiodarone is the drug of choice).
- Treatment of the underlying cause.
- Heart transplantation—If all above measures fail.

Q. What are the **complications of digoxin?** How to treat if toxicity of digoxin develops?

A. As follows:

1. Extracardiac:
   - Gastrointestinal: Anorexia, nausea, vomiting, diarrhea
   - Altered color vision (xanthopsia)
   - Others: Weight loss, confusion, headache, gynecomastia.
2. Cardiac:
   - Bradycardia
   - Multiple ventricular ectopics
   - Ventricular bigeminy
   - Atrial tachycardia with variable block
   - Ventricular tachycardia (bidirectional VT is mainly due to digitalis)
   - Ventricular fibrillation.

Treatment of digoxin toxicity:

- Digoxin should be stopped
- Serum electrolytes, creatinine and digoxin level should be checked.
- Correction of electrolytes, if any
- If bradycardia: IV atropine, sometimes pacing may be needed
- Correction of arrhythmia.

Q. What are the causes of **peripheral edema**?

A. As follows:

1. Pitting edema occurs in:
   - CCF
   - Hypoalbuminemia (nephrotic syndrome, protein loosing enteropathy or less protein intake, CLD)
   - Chronic venous insufficiency (varicose vein)
   - Drugs (calcium channel blockers, e.g. nifedipine, amlodipine)
   - Idiopathic (also called 'Fluid retention syndrome', common in women).
2. Non-pitting edema occurs in:
   - Myxedema.
   - Chronic lymphatic obstruction or lymphedema (e.g. filariasis, Milroy's disease).

Q. What are the causes of **lymphedema**?

A. As follows:

1. Primary:
   - Secondary to agenesis or hypoplasia
   - Hereditary (Milroy's disease)
   - Associated with Turner's syndrome, Noonan syndrome and Yellow nail syndrome.
2. Secondary:
   - Recurrent lymphangitis or cellulitis
   - Filariasis
   - Trauma
   - Tuberculosis
   - Neoplasm
   - Surgery (in the arm, it may be due to mastectomy)
   - Radiation
   - Burn.

Q. What are the causes of **bilateral** leg swelling?

A. As follows:

- Edema due to any cause (CCF, nephrotic syndrome and hypoproteinemia)
- Myxedema
- Some cases of lymphedema
- Acromegaly
- Inferior vena caval (IVC) obstruction (dilated tortuous veins in the lower limbs with upward flow)
- Iliac vein thrombosis
- Pregnancy
- Drugs (calcium channel blockers, such as nifedipine or amlodipine).

Q. What are the **causes of unilateral** leg swelling?

A. As follows:

- Lymphedema
- DVT
- Angioneurotic edema
- Ruptured Baker's cyst
- Chronic venous insufficiency.

Note

Unilateral swelling in arm may occur following mastectomy or radiation.

Q. What are the causes of **acute unilateral** leg swelling?

A. As follows:

- Deep venous thrombosis
- Ruptured Baker's cyst
- Cellulitis
- Trauma
- Angioedema.

Q. What is **high output** cardiac failure and **low output** cardiac failure? What are the **causes**?

A. As follows:

1. High output cardiac failure means "the heart fails to maintain sufficient circulation despite an increased cardiac output". Presentations are same as in low output cardiac failure except tachycardia, gallop rhythm, warm extremities with distended superficial veins. Causes are:
   - Severe anemia
   - Thyrotoxicosis
   - Arteriovenous fistula
   - Beriberi
   - Gram-negative septicemia
   - Paget's disease of the bone.
2. Low output cardiac failure means "the heart fails to maintain sufficient circulation with low cardiac output". Common causes are:
   - Ischemic heart disease
   - Multiple valvular lesion
   - Hypertension
   - Cardiomyopathy
   - Pericardial disease.

Q. What are the causes of **biventricular failure**?

A. As follows:

- Cardiomyopathy (commonly dilated cardiomyopathy)
- Myocarditis
- Ischemic heart disease (extensive myocardial infarction)
- Right sided heart failure secondary to left sided heart failure (e.g. MR, AS or AR)
- Hyperdynamic circulation (in severe anemia, thyrotoxicosis, arteriovenous shunt, beriberi)
- Myxedema (called myxedema heart)
- Multiple vulvular diseases.

Q. What are the causes of **left-sided heart failure (or pulmonary edema)**?

A. As follows:

- Systemic hypertension
- Acute myocardial infarction
- Aortic valvular disease (stenosis and regurgitation)
- Mitral regurgitation
- Cardiomyopathy
- Coarctation of aorta
- Rapid and excess infusion of fluid or blood or plasma
- Hyperdynamic circulation.

Q. What are the **cardinal features** of LVF?

A. As follows:

- Bilateral basal crepitations
- Gallop rhythm
- Pulsus alternans.

Q. How would you **manage** acute LVF (or acute pulmonary edema)?

A. As follows:

- Bed rest
- Propped up position
- High flow oxygen inhalation
- Diuretic—frusemide IV
- Morphine (if there is no contraindication)—10 to 20 mg IV slowly, if needed with antiemetic like metoclopramide or cyclizine
- ACE inhibitor
- If no response, inotropic agents like dopamine, dobutamine may be added
- Treatment of primary cause.

Q. What are the causes of **sudden** cardiac failure?

A. As follows:

- Acute myocardial infarction
- Arrhythmia (especially ventricular fibrillation)
- Circulatory overload (transfusion or infusion)
- Severe anemia
- Accelerated hypertension
- Dissecting aneurysm of aorta
- Massive pulmonary thromboembolism.

Q. What is **cardiac cachexia**?

A. Marked loss of weight or body mass that may occur in some cases of long standing moderate to severe cardiac failure is called cardiac cachexia.

It occurs commonly in patient more than 40 years with heart failure for more than 5 years. It is associated with high morbidity and mortality. Probable mechanisms are as follows:

- Malabsorption, anorexia and nausea due to intestinal venous congestion or edema, congestive hepatomegaly or toxicity of drugs (digoxin).
- Increased metabolic activity.
- TNF-α is increased, which is an important contributing factor for cachexia.
- Natriuretic peptide C is also increased.
- Poor tissue perfusion due to low cardiac output.

Q. What are the differences between **cardiac and bronchial asthma**?

A. As follows:

Features	Cardiac asthma	Bronchial asthma
1. History	Hypertension, IHD, valvular disease, family history of hypertension	History of previous attack of asthma, allergy or rhinitis, family history of asthma or allergy
2. Age	Usually elderly	Young, may be any age

Contd...

Contd...

3. Symptoms	» Dyspnea, cough with frothy sputum » Wheeze—rare » Sweating—common	» Dyspnea, cough with little mucoid sputum » Wheeze—common » Sweating—less
4. Signs	Pulse—may be pulsus alternans Blood pressure—high (if hypertensive) Heart— » Evidence of cardiomegaly (apex is shifted) » Gallop rhythm » Primary cause may be present (e.g. mitral or aortic valvular disease) Lungs— » Bilateral basal crepitation, later, extensive crepitations » No or little rhonchi	Pulse—may be pulsus paradoxus Blood pressure—normal, low in severe cases Heart— » Absent » No » No Lungs— » Plenty of rhonchi all over the lungs » No or little crepitations
5. CXR	» Perihilar opacities (bat's wing appearance) » Cardiomegaly	Relatively clear, evidence of infection may be present
6. ECG	LVH, myocardial infarction	Normal, only tachycardia may be present

HYPERTENSION

CHIEF COMPLAINTS

- Occasional headache, dizziness and giddiness for … months
- Chest pain for … months
- Sleeplessness for … months.

HISTORY

History of present illness: According to the patient's statement, he was reasonably alright … months back. Since then, he has been suffering from occasional headache, dizziness and giddiness. The headache mostly involves the occipital region and the back of the neck. It is pulsatile in nature, localized, mostly during the daytime, initiated by exertion or anxiety and relieved by sleeping. His headache is not associated with vertigo, nausea, vomiting, visual or hearing problem or facial pain. It is not preceded by any premonitoring symptoms. He also experiences occasional chest pain on moderate to severe exertion which is relieved by taking rest. There is no cough or breathlessness. For the last … months, he is experiencing sleeplessness and used to take sleeping pills. There is no history of fever, loss of consciousness, weight gain, muscular weakness, etc. His bowel and bladder habits are normal.

History of past illness

Family history

Personal history

Socioeconomic history

Drug history: Mention according to the statement of the patient.

GENERAL EXAMINATION

- Appearance: Anxious
- No anemia, cyanosis, jaundice, clubbing, edema, koilonychia, leukonychia, lymphadenopathy or thyromegaly
- Pulse: 84/min
- Blood pressure: 195/100 mm Hg
- Respiratory rate: 18/min
- Temperature: 98°F.

SYSTEMIC EXAMINATION

Cardiovascular System

- Pulse: 84/min, regular in rhythm, high volume and normal in character
- BP: 195/100 mm Hg
- JVP: Not engorged.

Precordium

Inspection:

- Visible cardiac impulse (mention if any).

Palpation:

- Apex beat is palpable, at left 5th intercostal space 8 cm from midsternal line, normal in character.
- Thrill: Absent.

Auscultation:

- All the heart sounds are normal
- There is no murmur or added sounds.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 45-year-old, businessman, smoker, nondiabetic, hailing from …, presented with occasional headache, dizziness and giddiness for … months. The headache mostly involves the occipital region and the back of the neck. It is pulsatile in nature, localized, mostly during the daytime, initiated by exertion or anxiety and relieved by sleeping. It is not associated with vertigo, nausea, vomiting, visual or hearing problem or facial pain. His headache is not preceded by any premonitoring symptoms. He also experiences occasional chest pain on moderate to severe exertion which is relieved by taking rest. There is no cough or breathlessness. For the last … months, he is experiencing sleeplessness and used to take sleeping pills. There is no history of fever, loss of consciousness, weight gain, muscular weakness, etc. His bowel and bladder habits are normal.

The patient smokes 1 pack of cigarette everyday for the last 25 years. His father is hypertensive and mother has diabetes. There is no history of renal disease in his family.

On examination, general examination—Mention as above.

Examination of cardiovascular system—Mention as above.

Other systems reveal no abnormalities.

My diagnosis is hypertension.

Q. What is the **cause of hypertension** in this patient?

A. This is most likely to be primary hypertension because there are no history or physical signs suggestive of a secondary cause.

Q. What **investigations** would you do in this patient?

A. As follows:

1. Routine:
   - Urine R/M/E: To see protein, RBC cast, pus cell, etc.
   - Blood urea, creatinine
   - Serum electrolytes
   - Fasting blood sugar
   - Serum lipid profile (total serum cholesterol, VLDL, LDL, HDL, triglyceride)
   - X-ray chest PA view
   - ECG
   - Echocardiogram.
2. Other investigation according to suspicion of cause:
   - If renal cause: Ultrasonogram of whole abdomen, IVU, CT scan of renal system, isotope renogram.
   - Cushing syndrome: Serum cortisol level, 24 hour urinary cortisol, ACTH, dexamethasone suppression test, etc.

- Pheochromocytoma: 24 hours urinary VMA, serum catecholamines
- Conn's syndrome: Plasma aldosterone and renin
- Coarctation of aorta: CT scan, aortogram.

RELATED QUESTIONS AND ANSWERS

Q. What is **hypertension**? What are the **types**?

A. Hypertension is defined as persistent rise of blood pressure above the normal range. JNC 7 recommends the following classification of blood pressure:

Type	Systolic BP (mm Hg)		Diastolic BP (mm Hg)
1. Normal	< 120	And	<80
2. Pre-hypertension	120 to 139	Or	80 to 89
3. Stage 1 hypertension	140 to 159	Or	90 to 99
4. Stage 2 hypertension	≥ 160	Or	≥ 100

According to British Hypertension Society, blood pressure is classified as follows:

Category	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Blood pressure		
Optimal	< 120 and	< 80
Normal	120 to 129 and/or	<85
High normal (equivalent to pre-hypertension)	130 to 139 and/or	85 to 89
Hypertension		
» Grade 1 (mild)	140 to 159 and/or	90 to 99
» Grade 2 (moderate)	160 to 179 and/or	100 to 109
» Grade 3 (severe)	≥ 180	≥ 110
Isolated systolic hypertension		
» Grade 1	140 to 149	< 90
» Grade 2	≥ 160	< 90

Q. When would you diagnose a patient to be **hypertensive**?

A. When systolic blood pressure is 140 or more or diastolic BP is 90 or more, the patient is diagnosed as hypertensive.

Note Remember the following points:

- A single reading is not sufficient. At least 3 readings in different times should be taken to label as hypertensive.
- BP should be measured at least 5 minutes after the patient has taken rest comfortably in sitting or supine position.
- BP should be measured at least 30 minutes after smoking or coffee ingestion.

Q. What is **white coat hypertension**?

A. When blood pressure is recorded in a hospital set up or in the physician's clinic, there may be transient rise in BP in a normal individual that gives a wrong perception of hypertension. This is called white coat hypertension. About 20% patient with apparent hypertension measured by a physician may have a normal BP, when it is recorded by automated devices at home.

Q. What is hypertensive **encephalopathy**?

A. It is characterized by very high BP with neurological abnormalities, such as severe headache, loss of consciousness, convulsion, paresthesia, transient disturbance of speech or vision, retinopathy, etc.

Q. What is hypertensive **emergency** and hypertensive **urgency**?

A. As follows:

- Hypertensive emergency or hypertensive crisis: It means severe elevation of BP (>180/120 mm Hg) with evidence of impending or progressive target organ dysfunction. It includes hypertensive encephalopathy (headache, irritability, confusion, altered mental status due to cerebrovascular spasm), hypertensive nephropathy (hematuria, proteinuria, progressive kidney dysfunction due to arteriolar necrosis and intimal hyperplasia of the interlobular arteries), intracranial hemorrhage, aortic dissection, pre-eclampsia, eclampsia, pulmonary edema, unstable angina or myocardial infarction. It needs substantial reduction of BP within 1 hour to avoid the risk of serious morbidity or death. Parenteral therapy is indicated in most hypertensive emergencies, especially if encephalopathy is present. At first BP should be reduced no more than 25% within minutes to 1 to 2 hours and then it should be gradually lowered to a target level of 160/100 mm Hg within 2 to 6 hours. Excessive reductions in pressure may precipitate coronary, cerebral or renal ischemia.
- Hypertensive urgency means severe elevation in BP without life-threatening target organ dysfunction. It is characterized by asymptomatic severe hypertension (systolic BP > 220 mm Hg or diastolic BP > 125 mm Hg), optic disk edema, progressive target organ complications and severe perioperative hypertension. Here BP must be reduced within a few hours. Parenteral drug therapy is not usually required and slow reduction of BP with relief of symptoms is the goal.

Q. What are the **causes** of hypertension?

A. As follows:

1. Primary or essential hypertension (95%).
2. Secondary (5%):
   a. Renal (commonest secondary cause):
      - Chronic glomerulonephritis
      - Chronic pyelonephritis
      - Diabetic nephropathy
      - Adult polycystic kidney disease
      - Renal artery stenosis.
   b. Endocrine:
      - Cushing's syndrome
      - Conn's syndrome (primary aldosteronism)
      - Pheochromocytoma
      - Congenital adrenal hyperplasia
      - Hyperparathyroidism
      - Primary hypothyroidism
      - Hyperthyroidism
      - Acromegaly.

c. Drugs:
- Alcohol
- Oral contraceptive pill
- Steroids
- NSAIDs
- Erythropoietin
- Sympathomimetics.

d. Others:
- Pre-eclamptia and eclampsia (toxemia of pregnancy)
- Pregnancy induced hypertension: Usually hypertension develops in the second half of pregnancy, which usually resolves after delivery (In contrast, hypertension developing in the first half of pregnancy or persisting after delivery is more likely to be essential hypertension)
- Coarctation of aorta
- Cerebral tumor.

Q. What are the **complications** of hypertension?

A. As follows:

1. Cardiovascular:
   - Ischemic heart disease
   - Acute left ventricular failure
   - Dissecting aneurysm.
2. Renal:
   - Renal failure.
3. Ocular:
   - Retinopathy.
4. Neurological:
   - CVD (intracerebral hemorrhage, sometimes infarction)
   - Subarachnoid hemorrhage
   - Hypertensive encephalopathy.

Q. What is **malignant hypertension**?

A. It is characterized by severe hypertension with diastolic BP > 130 mm Hg, associated with grade III or IV retinopathy (retinal hemorrhage or exudates and papilledema) and renal failure or encephalopathy. It is a rare complication of hypertension. There is accelerated microvascular damage with fibrinoid necrosis in the walls of small arteries and arterioles and intravascular thrombosis. This may lead to LVF and if untreated, death occurs within months.

Treatment: Slow, controlled reduction of BP over a period of 24 to 48 hours is ideal (Rapid reduction is avoided, as it reduces tissue perfusion and can cause cerebral damage including occipital blindness, may even precipitate coronary or renal insufficiency).

- Complete rest.
- Oral antihypertensive is sufficient to control the blood pressure.
- Sometimes IV or IM labetalol, IV glycerin trinitrate, IM hydralazine, IV nitroprusside may be given with careful supervision.

Q. What is **refractory hypertension?** What are the **causes?**

A. When there is no response to antihypertensive drugs, it is called refractory hypertension. The causes are:

- Poor compliance to drug therapy (the most common cause)

- Inadequate therapy
- Failure to recognize an underlying cause like renal artery stenosis or pheochromocytoma.

JNC 7 has defined **resistant hypertension** as, "the failure to reach BP control in patients who are adherent to full doses of an appropriate three drug regimen including a diuretic". The following things should be carefully excluded:

- Improper BP measurement.
- Volume overload which may be due to excess sodium intake, renal disease or inadequate diuretic therapy.
- Inadequate dose, inappropriate combination of drugs or nonadherence.
- Drug induced hypertension like NSAIDs, steroid, oral contraceptive pills, cyclosporine, tacrolimus, erythropoietin, etc.
- Other secondary causes of hypertension.
- Associated conditions like obesity, excess alcohol intake, etc.

Q. What are the **grades** of hypertensive retinopathy?

A. Four grades (Keith-Wagener-Barker classification):

- **Grade I:** Thickening of arterial wall, increase tortuosity, narrowing of arteriole and increased light reflex (silver wiring).
- **Grade II:** Grade I plus AV nipping and reduction of arterial calibre in comparison to vein (normal ratio of V:A = 3:2).
- **Grade III:** Grade II plus cotton wool exudate and flame-shaped hemorrhage.
- **Grade IV:** Grade III plus papilloedema (Grade III and IV indicate malignant hypertension).

Q. What **history** would you take in a patient with hypertension?

A. As follows:

- Age: If young, likely to be secondary cause. If elderly, likely to be primary.
- Family history: Family history of hypertension, hyperlipidemia, diabetes mellitus, obesity, etc. may be present in case of primary hypertension. In some secondary hypertension, there may be positive family history, e.g. polycystic kidney disease.
- Past medical history: Previous history of renal disease (hematuria, UTI, renal trauma, pain, pyelonephritis), toxemia of pregnancy (in female).
- Drug history: Prolong use of NSAIDs, steroids, oral contraceptive pill, etc.
- History of smoking.
- Symptoms to find out the secondary casue:
  a. Symptoms of renal disease like polyuria, frequency, hematuria, loin pain.
  b. Paroxysmal attack of headache, palpitation, flushing and sweating (pheochromocytoma).
  c. Polyuria, polydipsia, extreme muscular weakness, tingling (Conn's syndrome).
  d. Weight gain, hirsutism, striae, menstrual abnormality in female (Cushing syndrome).
  e. Claudication and cramp in lower limbs in a young patient (coarctation of aorta).
  f. Frequent attack of headache, vomiting, visual disturbance, neurological features (intracranial tumor).

Q. What physical **signs** would you look for in a patient with hypertension?

A. As follows:

- Puffy face: Renal failure.
- Central obesity with plethoric moon face, hirsutism, striae: Cushing syndrome.

- Pulse: Bradycardia suggests raised intracranial pressure, feeble pulse in lower limbs with radiofemoral delay found in coarctation of aorta.
- Blood pressure: High BP in upper limbs, but low in lower limbs suggest coarctation of aorta.
- Anemia: Suggests chronic renal failure.
- Edema: May be present in renal failure.
- Cardiovascular system: Apex may be heaving and shifted (left ventricular hypertrophy or enlargement), murmur may be present in coarctation of aorta.
- Abdomen: Bilateral renal mass in polycystic kidney disease, renal bruit in renal artery stenosis.
- Fundoscopy to see retinal change.
- Other finding according to suspicion of cause like intracranial space occupying lesion.
- Bed side urine examination for hematuria and proteinuria.

Q. **Whom** should you treat for hypertension? What is the **target** BP?

A. The following patients should be treated with drugs and lifestyle change:

- Malignant hypertension.
- All patients with a sustained (at least 2 visits) systolic BP ≥ 160 mm Hg and/or diastolic BP ≥ 100 mm Hg (grade 2 or 3 hypertension).
- Patients with systolic BP 140 to 159 mm Hg and/or diastolic BP 90 to 99 mm Hg (grade 1 hypertension) with 10 year cardiovascular (CVD) risk of at least 20% or existing CVD, target organ damage or diabetes mellitus.
- Isolated systolic hypertension (systolic BP >160 mm Hg).

In patients with grade 1 hypertension without 10 year CVD risk of at least 20% or target organ damage should get lifestyle modification and yearly reassessment. Those who have systolic BP < 140 and diastolic BP < 90 mm Hg should be reassessed in 5 years.

The target BP is ≤ 140/90 mm Hg. But in diabetes mellitus, it should be < 130/80 mm Hg and in case of proteinuria, the target is <125/75 mm Hg.

Q. How to **treat** hypertension?

A. As follows:

1. General measures (**non-drug treatment** of hypertension):
   - Salt restriction (< 6 g/day).
   - Smoking should be stopped.
   - Weight reduction in obese patients (BMI should be < 25 kg/m^2).
   - Dietary modification: Low fat and saturated fat and increase fruits and vegetables, also oily fish.
   - Regular exercise (at least 30 minutes dynamic exercise daily).
   - Reduction of anxiety and tension.
   - Control of diabetes mellitus.
   - Restriction of tea and coffee.
   - Restriction of alcohol intake (< 21 units/week for men and <14 units/week for women).
   - Control of other modifiable risk factors.
2. Drug treatment:
   - Diuretic: Thiazide (bendroflumethiazide or cyclopenthiazide).
   - ACE inhibitors: Enalapril, lisinopril, ramipril.
   - ARB: Losartan, valsartan, irbesartan.
   - Calcium channel blocker: Amlodipine, nifedipine, diltiazem, verapamil.
   - Beta blocker: Atenolol, metoprolol, bisoprolol.
   - Combined alpha and beta blocker: Labetalol, carvedilol.
   - Alpha blocker: Prazosin, doxazosin.

- Renin inhibitor: Aliskiren (this is a newly introduced drug).
- Others: Methyldopa (specially for pregnancy).

3. Management of primary cause, if any.

Note

Adjuvant therapy-antiplatelet (aspirin) may be added with antihypertensive drugs especially in patients over 50 years. Also statin may be added. Both of these, reduces cardiovascular risk.

TREATMENT OF HYPERTENSION IN SPECIFIC CONDITIONS

Hypertension in bronchial asthma:

- Drugs like diuretics, calcium channel blocker, ARB, ACE inhibitor (it may cause cough).
- Avoid β-blockers.

Hypertension in chronic kidney disease: (Target BP is < 130/80 mm Hg).

- ACE inhibitors and ARB may delay progression of kidney disease (if creatinine is >2.5 mmol/L, these should be avoided).
- Calcium channel blocker may be used.
- Thiazide diuretic may be replaced with loop diuretics.

Hypertension in pregnancy:

- Methyldopa or labetalol.
- Other drugs: Calcium channel blocker (nifedipin) may be used. Sometimes, β-blocker may be used but should be avoided in first trimester.
- ACE inhibitor is contraindicated.
- Diuretic is also avoided (there is risk of uteroplacental blood flow reduction).

Hypertension in diabetes mellitus:

- ACE inhibitor, ARB, calcium channel blocker may be used.
- Avoid thiazide (it aggravates diabetes).
- Avoid β-blocker in patient who is on insulin (it masks symptoms of hypoglycemia).

Hypertention in peripheral vascular disease:

- Calcium channel blocker.
- Alpha blocker may be an alternative.
- Avoid β-blocker. ACE inhibitor should be used carefully (as the patient may have renal artery stenosis also).

Hypertension in dyslipidemia:

- Alpha blocker, ACE inhibitor, ARB, calcium channel blocker.
- Avoid β-blocker and diuretic (which worsen lipid profile).

Hypertension in psoriasis:

- Calcium channel blocker.
- Avoid β-blocker, ACE inhibitor (which aggravates).

Hypertension in angina:

- Beta blocker, calcium channel blocker, nitrate.

Hypertension in elderly:

- Thiazide (it is avoided if coexistent diabetes mellitus and gout).
- Calcium channel blocker.

Q. How would you treat **hypertension in pregnancy**?

A. As follows:

- Methyldopa or labetalol.
- Calcium channel blocker like nifedipine may also be used.
- More severe hypertension or eclampsia may be treated with intravenous hydralazine, even termination of pregnancy may be required.

SUBACUTE BACTERIAL ENDOCARDITIS

CHIEF COMPLAINTS

- Fever for … months
- Chest pain and palpitation for … months
- Difficulty in breathing for … months
- Weight loss for … months.

HISTORY

History of present illness: According to the patient's statement, he was reasonably alright … months back. Since then, he has been suffering from low grade, continued fever, sometimes associated with chills and rigor, also with profuse sweating, subsides only with paracetamol, highest recorded temperature was 101°F. He also complains of central chest pain, sharp in nature without any radiation, does not aggravate by cough or movement of the chest. He also experiences occasional palpitation, associated with difficulty in breathing after mild to moderate exertion for the last … months, which are relieved by taking rest. There is no history suggestive of orthopnea or paroxysmal nocturnal dyspnea.

For the last … months, the patient also experiences malaise, generalized weakness, arthralgia, myalgia, anorexia and substantial loss of weight.

There is no history of unconsciousness, hematuria or loin pain (differentiates from embolic phenomenon). He does not give any history of dental procedures or cardiac or other surgery or instrumental procedure (catheterization, colonoscopy, cannula, etc.) or any history of intravenous drug abuse. His bowel and bladder habits are normal.

History of past illness: He has been suffering from some valvular heart disease for several years (mention, if there are other histories like cardiac surgery).

Family history

Personal history

Socioeconomic history

Drug history: Mention according to the statement of the patient.

GENERAL EXAMINATION

- Appearance: Ill looking, emaciated and toxic (there may be brownish pigmentation of face and limbs called Cafe-au-lait pigmentation).
- Moderately anemic.
- Generalized clubbing: Involving all the fingers and toes.
- There are two splinter hemorrhages in the left index finger.
- No cyanosis, jaundice, koilonychia, leukonychia, lymphadenopathy or thyromegaly.
- Pulse: 110/min.
- Blood pressure: 95/75 mm Hg.
- Respiratory rate: 28/min.
- Temperature: 100°F.
- (If present, mention the following: Osler's node, Janeway lesion, infarction at the tip of fingers or toes, petechiae on the dorsum of hands or feet or other parts.)

SYSTEMIC EXAMINATION

Cardiovascular System

- Pulse: 110/min, regular in rhythm, normal in volume and character.
- BP: 95/75 mm Hg.
- JVP: Not engorged.

Precordium

Inspection:

- Visible cardiac impulse (mention if any).

Palpation:

- Apex beat is palpable, at left 5th intercostal space 8 cm from midsternal line, normal in character.
- Thrill: Present, in … space, diastolic (or systolic) in nature.

Auscultation:

- First heart sound is soft in all the areas, 2nd heart sound is normal in all the areas.
- There is a systolic (or diastolic) murmur, in … intercostal space, with (or without) radiation (mention accordingly).
- Mention any valvular or cardiac lesion according to your finding.

Abdomen

- Spleen is just palpable.
- No other abnormality in abdominal examination.

Eye

- Roth's spot (white centered retinal hemorrhage).

Nervous System

- There is no change (but if there history of cerebral embolism, there may be signs of hemiplegia).

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 28-year-old, student, normotensive, nondiabetic, nonsmoker, presented with fever for … months, which is low grade, continued, sometimes associated with chills and rigor, also with profuse sweating, subsides only with paracetamol, highest recorded temperature was 101°F. He also complains of central chest pain, sharp in nature without any radiation, does not aggravate by cough or movement of the chest. He also experiences occasional palpitation, associated with difficulty in breathing after mild to moderate exertion for the last … months, which are relieved by taking rest. There is no history suggestive of orthopnea or paroxysmal nocturnal dyspnea. For the last … months, the patient also experiences malaise, generalized weakness, arthralgia, myalgia, anorexia and substantial loss of weight. There is no history of unconsciousness, hematuria or loin pain (differentiates from embolic phenomena). He does not give any history of dental procedures or cardiac or other surgery or instrumental procedure (catheterization, colonoscopy, cannula, etc.) or any history of intravenous

drug abuse. His bowel and bladder habits are normal. He has been suffering from some valvular heart disease for several years. There is no family history of such illness. He used to take frusemide, propranolol and vitamins prescribed by the local physicians.

On examination, general examination—mention as above.

Examination of cardiovascular system—mention as above.

Examination of other systems reveals no abnormalities.

My diagnosis is subacute bacterial endocarditis with valvular lesion (mention which one is present).

Q. Why your first diagnosis is SBE?

A. Because:

- The patient is a known case of heart disease (mention which one)
- Fever which is not responding to multiple antibiotics
- Associated features like clubbing, splinter hemorrhage, cardiac murmur, splenomegaly, Roth's spot, etc.

Q. What are your differential diagnoses?

A. As follows (any cause of PUO should be considered. Common possibilities are):

- Tuberculosis
- Kala-azar
- Malaria
- Collagen disease (SLE)
- Lymphoma.

Note Remember, in any patient with prolong fever, which is not responding to usual therapy, SBE should be considered if there are:

- History of previous cardiac lesion
- Appearance of a new murmur
- Change in the nature of a pre-existing murmur.

Q. What investigations should be done to diagnose SBE?

A. As follows:

- Hb%, TC, DC, ESR (normochromic normocytic anemia, neutrophil leukocytosis, high ESR may be present).
- Serum CRP (increased. It is more reliable than ESR in monitoring progress).
- Blood culture (both aerobic and anaerobic)—3 cultures from different sites at 1 hour apart during peak fever, taken after all aseptic measures (10 to 20 mL blood is taken each time). If possible, both aerobic and anaerobic cultures should be done. In some cases, fungal culture should also be done. 10% are culture negative.
- Echocardiography (to see vegetation, valvular lesion or congenital anomaly). Transesophageal echocardiography is more sensitive than transthoracic echocardiography. TOE is mandatory in case of doubtful case, prosthetic or pacemaker endocarditis or when an abscess is suspected. The sensitivity of transthoracic echo is about 55 to 65%, but that of transesophageal echo is more than 90%.
- Urine R/M/E (hematuria and proteinuria may be present).
- CXR P/A view (may show cardiomegaly or evidence of cardiac failure).
- ECG: May show prolong PR interval (AV block due to aortic root abscess formation) and occasionally infarction (due to emboli).
- Urea and creatinine.

RELATED QUESTIONS AND ANSWERS

Q. What are the **predisposing factors or causes** of SBE?

A. Causes or predisposing factors are as follows:

- Rheumatic valve lesion (e.g. AR, MR, etc.).
- Congenital heart disease (VSD, PDA, bicuspid aortic valve, coarctation of aorta, TOF. SBE is rare in ASD, PS, MS, AS).
- Prosthetic valve.
- Dental extraction.
- Instrumentation (catheterization, sigmoidoscopy, cystoscopy, endoscopy, cannulation).
- Cardiac surgery or cardiac catheterization.
- IV drug abuse (right sided endocarditis is more common, especially involves tricuspid valve).

Q. What are the **organisms** causing infective endocarditis?

A. As follows:

1. Subacute bacterial endocarditis:
   - *Streptococcus viridans* (*S. sanguis*, *S. mitis*)—the most common (35 to 50%)
   - *Enterococcus faecalis*, *E. faecium*
   - *S. bovis*, *S. milleri* and other streptococci
   - *S. aureus* or *epidermidis*
   - Diphtheroids
   - HACEK organism (*Haemophilus, Actinobacillus, Cardiobacterium hominis, Eikenella, Kingella*).
2. Acute bacterial endocarditis:
   - *S. aureus* (the most common)
   - *Pseudomonas*
   - *Candida*
   - *S. pneumoneae*
   - *Neisseria gonorrhoea*
3. Postoperative endocarditis:
   - *S. albus*
   - *Candida*
   - *Aspergillus*
   - All other organisms causing subacute and acute endocarditis.

Q. What are the **signs in the hand** in SBE?

A. As follows:

- Clubbing (a late sign).
- Osler's node (small painful violaceous raised nodule, 0.5 to 1.5 cm, present on the tip of the fingers, palmar aspect and tip of the toes, probably due to the product of vasculitis or septic embolism).
- Splinter hemorrage (subungual).
- Janeway lesion (large painless erythematous macules on the palm and sole).
- Patechial hemorrhage.
- Infarction due to embolism.

Q. What is **vegetation**?

A. It is a small solid mass composed of platelet, fibrin and organism, occurring at the site of endothelial damage in the valve or endocardium. It may result in embolism.

Q. What are the **differences** between acute and subacute bacterial endocarditis?

A. As follows:

Parameter	Acute bacterial endocarditis	Subacute bacterial endocarditis
1. Organism	Highly virulent	Less virulent
2. Cardiac lesion	Usually no previous cardiac lesion	Cardiac lesions are usually present
3. Presentations	Sudden onset with high temperature, chill and rigor	Insidious onset
4. Mortality	High	Low
5. Peripheral signs like Osler's node, Janeuray lesion, etc.	Absent	Present

Q. What are the **Duke criteria** for the diagnosis of infective endocarditis?

A. As follows:

Major criteria:

1. Positive blood culture:
   - Typical organism from 2 cultures or,
   - Persistently positive blood cultures defined as: Positive blood cultures obtained more than 12 hours apart or, positive culture in all three or majority of four or more blood samples with the first and last one taken over 1 hour apart or,
   - Single blood culture of *Coxiella burnetii* or positive serological test for Q fever with phase 1 IgG antibody titer of >1:800.
2. Endocardium involvement:
   - Positive echocardiogram (vegetation, abscess, new partial dehiscence of prosthetic valve) or,
   - New valvular regurgitation (worsening or change in murmur is not sufficient).

Minor criteria:

- Predisposition (cardiac lesion, IV drug abuse).
- Fever 38ºC or more.
- Vascular signs (major arterial emboli, septic arterial emboli, mycotic aneurysm, intracranial hemorrhage, Janeway lesion).
- Immunological signs (Osler's node, Roth's spot, glomerulonephritis, rheumatoid factor).
- Positive blood culture that does not meet major criteria.
- Positive echocardiogram that does not meet major criteria.

Diagnosis:

- Definite infective endocarditis: 2 major or 1 major and 3 minor or 5 minor criteria (if no major criteria is met).
- Possible infective endocarditis: 1 major and 1 minor or 3 minor criteria.

Note

It has a sensitivity of about 80%.

Q. What are the **immunological features** of SBE?

A. Osler's node, Roth's spot, glomerulonephritis and rheumatoid factor.

Q. What are the causes of **culture negative endocarditis?**

A. As follows:

- Prior antibiotic treatment (common cause).
- Fungal, yeast, anaerobic infection or Q fever (needs special culture).
- Right sided endocarditis.
- Non-infective endocarditis: Libmann Sac (non-bacterial verrucous endocarditis in SLE, which is usually associated with antiphospholipid antibody syndrome), marantic endocarditis (non-bacterial thrombotic or verrucous endocarditis found in malignancy, such as bronchial carcinoma).

Q. What are the **complications** of SBE?

A. As follows:

- Heart failure (LVF is a common cause of death).
- Valve destruction, regurgitation, obstruction.
- Aortic root abscess, may lead to prolongation of PR interval or even complete AV block.
- Systemic embolism.
- Right sided endocarditis usually involves the pulmonary valve and may cause septic pulmonary emboli, occasionally with infarction and lung abscess.
- Vasculitis.

Q. How to **treat** SBE?

A. As follows:

1. Antibiotic:
   - Ideally antibiotic should be given according to culture and sensitivity. However, treatment should be started as soon as the blood sample is sent for culture and sensitivity. In subacute cases, benzylpenicillin 1.2 g IV 4 hourly and gentamicin 1 mg/kg IV 8 hourly for 4 weeks is given. In acute cases, flucloxacillin 2 g IV 6 hourly is added to cover staphylococci. In case of penicillin allergy, a prosthetic valve or suspected methicillin-resistant *Staphylococcus aureus* (MRSA) infection, triple therapy with vancomycin, gentamicin and oral rifampicin should be considered.
   - Another regimen of empirical therapy—vancomycin 1 g 12 hourly IV with ceftriaxone 2 g every 24 hours is a good choice pending definitive diagnosis.
   - For viridans streptococci, ceftriaxone 2 g once daily IV or IM for 4 weeks is effective. In penicillin allergic patients, vancomycin 15 mg/kg IV 12 hourly for 4 weeks is given. In prosthetic valve endocarditis, penicillin for 6 weeks and gentamicin for 2 weeks should be given.
   - For HACEK organisms, ceftriaxone 2 g IV once daily for 4 weeks are given. If prosthetic valve is involved, then treatment should be given for 6 weeks.
   - Q fever endocarditis needs prolong treatment with doxycycline and rifampicin or ciprofloxacin. Even then, organisms are not always eradicated. Valve surgery is often required.
2. Other antibiotic may be given according to the suspicion of the cause.
3. Any source of infection (e.g. a tooth with an apical abscess) should be removed as soon as possible.
4. Other supportive treatment should be given accordingly.
5. Treatment of the underlying cause like valvular disease.

Q. What **preventive** measures should be taken during dental procedure?

A. Routine antibiotic prophylaxis prior to dental procedure is no longer recommended as this has not been proven to be effective. However, in few high risk cases antibiotic prophylaxis may be considered. These are:

- Prosthetic cardiac valve.
- Previous infective endocarditis.

- Congenital heart disease (CHD)—unrepaired cyanotic CHD, completely repaired CHD with prosthetic material or device or repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device.
- Cardiac transplantation recipient in whom cardiac valvulopathy develops.

Drugs used for prophylaxis:

- Amoxicillin 2 g 1 hour before procedure.
- If penicillin allergy—clindamycin 600 mg or cephalexin 2 gm or azithromycin or clarithromycin 500 mg 1 hour before procedure.
- If the patient is unable to take by mouth, parenteral therapy may be given with ampicillin 2 g IV or IM 30 minutes before the procedure. In case of penicillin allergy, clindamycin 600 mg IV 1 hour before procedure or cefazolin 1 g IM or IV 30 minutes before procedure.

Q. What are the **indications of cardiac surgery** in infective endocarditis?

A. Surgery (debridement of infected material and valve replacement) is indicated in following conditions:

- Progressive heart failure from valve damage
- Valvular obstruction
- Repeated embolization
- Fungal endocarditis
- Persistent bacteremia in spite of adequate antibiotic therapy
- Myocardial abscess
- Endocarditis of prosthetic valve
- Large vegetation in left sided valve.

Q. What is the **prognosis**?

A. 30% mortality with staphylococci, 14% with bowel organisms, 6% with sensitive streptococci.

Note Remember the following points:

- Infective endocarditis typically occurs at the site of pre-existing endocardial damage. However, if the organism is virulent or aggressive (e.g. *Staphylococcus aureus*), it may occur in a previously normal heart.
- *S. viridans* is the most common cause of subacute endocarditis.
- *S. aureus* is the most common cause of acute endocarditis. It originates from skin infection, abscess, vascular access sites or from intravenous drug misuse. It is highly virulent and can cause endocarditis in normal heart. It usually causes florid vegetations, rapid valve destruction and abscess formation.
- Other causes of acute endocarditis are *S. pneumoniae*, *S. pyogenes*, *S. lugdenensis*, etc.
- The most common cause of endocarditis after cardiac surgery is *S. epidermidis*.
- Prosthetic valve endocarditis—in early infection (<2 months) common organism is *Staphylococcus* (this is usually acquired at the time of surgery and has a poor prognosis). In late case (> 2 months), commonest is *Streptococcus* and is acquired hematogenously. Aortic valve prosthesis is more prone to develop endocarditis than mitral valve.
- Right sided endocarditis is common in IV drug users, also sometimes in patients receiving central venous catheter. The most common organism is *Staphylococcus aureus*. Also, other organisms like *Streptococcus pneumoniae* and fungus may be responsible. It mainly affects the tricuspid valve, rarely pulmonary valve. Prognosis is relatively better. It may cause septic pulmonary emboli, occasionally with infarction and lung abscess.
- *S. bovis* and *S. milleri* are associated with large bowel neoplasms.
- In Q fever endocarditis (by *Coxiella burnetii*) and brucellosis, usually aortic valve is involved. Both have history of contact with farm animals.
- Hepatomegaly is common in Q fever endocarditis.

RHEUMATIC FEVER

CHIEF COMPLAINTS

- Migrating polyarthritis involving bigger joints (knee, ankle, elbow) for … days
- Fever for … days
- Palpitation, chest pain … for days
- Malaise, weakness, fatigue for … days.

HISTORY

History of present illness: According to the patient's statement, she was quite fit and well … days back. Then she suffered from sore throat from which she recovered completely within a few days. After … days, she developed severe joint pain. Initially, it involved the right knee joint, but then sequentially the right ankle, left knee, left ankle and elbow joints were involved. The joints are swollen, red and very painful, even with mild movement. The smaller joints are not involved. There was no morning stiffness.

The patient also complains of fever, which is high grade, continued and reduces with antipyretic drugs. It is not associated with chill and rigor, but there is profuse sweating. She also complains of palpitation, chest pain, malaise, fatigue, weakness during her disease period. There is no history of abnormal or involuntary movement (chorea) or skin changes. Her bowel and bladder habits are normal. She denied any history of diarrhea, sexual exposure, skin rash, mouth ulcer, uveitis or any urinary complaint.

History of past illness

Family history

Personal history

Socioeconomic history

Drug history: Mention according to the patient's statement.

GENERAL EXAMINATION

- Appearance: Ill looking
- Built: Average
- Nutrition: Average
- Anemia: Mildly anemic
- No jaundice, cyanosis, clubbing, leukonychia, koilonychia, edema or dehydration
- Pulse: 110/min
- BP: 130/75 mm Hg
- Temperature: 39°C
- Respiratory rate: 24/min
- No lymphadenopathy, thyromegaly, etc.

(Mention any other sign of rheumatic fever, if present).

SYSTEMIC EXAMINATION

Cardiovascular System

- Pulse: 110/min.
- BP: 130/75 mm Hg.
- Neck vein: Not engorged.

Precordium: (findings depend on pancarditis).

Inspection:

- Visible cardiac impulse in mitral area.

Palpation:

- Mention the position of apex and other findings as present in your case.

Auscultation:

- First and second heart sounds: Normal
- No murmur is present
- No added sound.

Locomotor Examination: (Involved joint, e.g. knee joint):

Inspection:

- Swollen (parapatellar fossa are full)
- Red.

Palpation:

- Local temperature: Increased
- Tenderness: Present
- Fluctuation test: Positive
- Movement: Restricted due to pain.

Skin changes (such as subcutaneous nodule, erythema marginatum).

Alimentary system—no abnormality.

Respiratory system—no abnormality.

Nervous system (abnormal movements such as chorea).
(Mention according to your findings).

SALIENT FEATURES

Ms …, 18-year-old, student, normotensive, nondiabetic, nonsmoker, hailing from …, had suffered from sore throat for a few days about … days ago with complete recovery. After … days, she developed migrating, inflammatory, polyarthritis of large joints which sequentially involved the right knee, right ankle, left knee, left ankle and elbow joints. He felt pain even with mild movement. The small joints are not involved and there was no morning stiffness. The patient also had high grade, continued fever without chill or rigor but associated with profuse sweating. She also complains of palpitation, chest

pain, malaise, fatigue, weakness during her disease period. There is no history of abnormal or involuntary movement (chorea) or skin changes. Her bowel and bladder habits are normal. She denied any history of diarrhea, sexual exposure, skin rash, mouth ulcer, uveitis or any urinary complaint. She used to take some painkiller the name of which she could not mention. There is no family history of such illness.

On examination, general examination—mention as above.

Examination of cardiovascular system—mention as above.

Other systems reveal no abnormalities.

My diagnosis is acute rheumatic fever.

Q. What are your **differential diagnoses**?

A. As follows:

- Infective arthritis (viral or bacterial)
- Juvenile chronic arthritis (juvenile <16 years)
- SLE
- Seronegative arthritis (reactive arthritis, Reiter's syndrome)
- Rheumatoid arthritis.

Q. **Why** do you think this is a case of rheumatic fever?

A. This young patient has a history of sore throat followed by a latent period and then she developed migrating, inflammatory polyarthritis involving the large joints without any deformity. All these are in favor of acute rheumatic fever.

Q. **Why not** this is a case of SLE?

A. Because , in this case, arthritis is fleeting is nature involving the bigger joints that is not common in SLE. Also, other criteria of SLE like skin rash, butterfly rash, mouth ulcer, alopecia, menstrual irregularity, etc. are absent.

Q. **Why not** this is a case of JIA?

A. JIA occurs in young patient less than 16 years of age. The arthritis is not fleeting in nature. Also, in JIA there is usually deformity of the joints.

Q. **Why not** this is a case of reactive arthritis or Reiter's syndrome?

A. Reiter's syndrome is characterized by triad of iritis, arthritis and urethritis. But the patient does not have history of involvement of the eyes or urinary tract. Also, it occurs after an episode of diarrhea or urethritis which are not present here.

Q. What **investigations** will you do in this patient?

A. As follows:

- Hb, TC, DC, ESR (high ESR and leukocytosis)
- C-reactive protein (CRP is high)
- Antistreptolysin O (ASO) titre (may be high, in adult > 200, in children > 300)
- Throat swab culture (to find *Streptococcus* beta hemolyticus)
- Chest X-ray (cardiomegaly, pulmonary edema may be present)
- ECG
- Echocardiography (to see valve abnormality and cardiomegaly)
- Others—RA factor (to exclude rheumatoid arthritis) and ANA (to exclude SLE), if needed.

RELATED QUESTIONS AND ANSWERS

Q. What is **rheumatic fever?** What is the **mechanism or pathogenesis**?

A. Rheumatic fever is a multisystem disorder, occurring as a sequelae to pharyngitis by group A β hemolytic *Streptococcus*. It is due to autoimmune reaction between the antigen (M protein) of *Streptococcus* β hemolyticus and cardiac myosin and sarcolemal membrane protein (laminin). As a result, antibody is produced against streptococcal enzyme, causing inflammation in the endocardium, myocardium and pericardium as well as joints and skin. There is formation of "Aschoff's nodule" in heart, which is pathognomonic of rheumatic fever.

Q. What are the usual **presenting complaints** of a patient with rheumatic fever?

A. Rheumatic fever (RF) usually occurs in children and young adults. Peak incidence is 5 to 15 years. It usually recurs unless prevented. There is usually a history of sore throat by group A β hemolytic *Streptococcus* 1 to 3 weeks prior to the fever.

Features are:

- Migrating (fleeting), non-deforming polyarthritis involving the large joints (knee, ankle and elbow) and wrists with fever, which may be continuous, high grade is the presenting feature in 75% cases.
- Palpitation and chest pain (due to carditis in 50% cases).
- Skin rash (erythema marginatum), subcutaneous nodules.
- Involuntary movement (chorea in 10 to 30% cases).
- Malaise, weakness and fatigue.

Q. Which **joints** are commonly involved in acute rheumatic fever?

A. Commonly large joints like ankle, wrist, knee and elbow (usually does not involve small joints of the hands and feet, rarely involves hip joint).

Q. What are the **diagnostic criteria** of rheumatic fever?

A. It is diagnosed by revised **Jones' criteria**. Following an attack of *Streptococcus pharyngitis*, there is usually a latent period of 1 to 3 weeks.

1. Major criteria:

- Carditis
- Shifting polyarthritis
- Rheumatic chorea
- Erythema marginatum
- Subcutaneous nodule.

2. Minor criteria:

- Fever
- Arthralgia
- Previous history of rheumatic fever
- High ESR or CRP
- Leukocytosis
- First or second degree AV block in ECG.

In addition, **supportive evidence of previous streptococcal infection**, like recent streptococcal infection, history of scarlet fever, raised ASO titer (>200) or other streptococcal antibody titer (anti-DNAse or antihyaluronidase) or positive throat swab culture.

Diagnosis is made by two or more major criteria, or one major and two or more minor criteria plus supportive evidence of streptococcal infection.

Q. What are the **signs** of carditis?

A. Rheumatic fever can cause carditis involving all the layers of the heart (endocardium, myocardium and pericardium), called pancarditis.

Signs of endocarditis:

- Soft heart sounds
- Pansystolic murmur (due to MR)
- Mid diastolic murmur (Carey Coombs murmur)
- Early diastolic murmur (due to AR which is due to valvulitis with nodules on the valve).

Signs of myocarditis:

- Tachycardia
- Soft heart sounds, S_3 gallop
- Cardiomegaly
- Features of heart failure.

Signs of pericarditis:

- Pericardial rub (patient usually complains of chest pain)
- Pericardial effusion may be present.

Q. What is **'Aschoff's nodule'**?

A. It is a granulomatous nodule composed of central fibrinoid necrosis and multinucleated gaint cells, with surrounding macrophages and T-lymphocytes. It occurs throughout the heart and is common in the interstitial tissue close to the small blood vessels situated beneath the endocardium of the left ventricle. It is pathognomonic of RF.

Q. What is **erythema marginatum**?

A. It is a transient, geographical type rash with pink or red raised edges, round margin and clear center. It may coalesce into crescent or ring shaped patches. The rash blanches on pressure. It is found mostly on the trunk and proximal limbs (not in face). It occurs in about 10% cases.

Q. What is **subcutaneous nodule?**

A. These are small, mobile, firm, painless, pea-shaped nodules, felt over bony prominences, tendons or joints on the extensor surface. Occurs in 10 to 15% cases.

Q. What is **Sydenham's chorea** (St Vitus' dance)?

A. It is a neurological manifestation of acute RF, which usually occurs after 3 months of an acute attack, when almost all other signs have disappeared.

- It occurs in one-third of cases, common in children and adolescents, especially in female of 5 to 15 years of age.
- Usually associated with emotional instability, irritability, inattentiveness and confusion.

- It may occur without any feature of acute RF. Carditis is common and may be the first manifestation.
- Speech may be explosive and halting.
- ESR, ASO titre and CRP are usually normal.
- Rheumatic chorea is usually self-limiting, and recovers within few months.
- Relapse may occur only in few cases, occasionally during pregnancy (called chorea gravidarum) or in those who use oral contraceptive pill.
- Treatment—sedation (haloperidol) along with other treatment and prophylaxis of rheumatic fever.
- 25% of cases develop chronic rheumatic heart disease in course of time.

Q. What are the **signs of activity** in rheumatic fever?

A. As follows:

- Persistent fever
- Tachycardia
- High ESR
- Leukocytosis
- Evidence of carditis.

Q. How to **treat** acute RF?

A. As follows:

1. Complete bed rest (until disease activity resolves).
2. Oral phenoxymethylpenicillin 250 mg 6 hourly for 10 days or single injection of benzathine penicillin 1.2 million units, deep IM in the buttock (to eliminate the streptococcal infection). Erythromycin may be given if allergic to penicillin.
3. Analgesic (to relieve pain). Aspirin 60 mg/kg per day in divided doses. Higher dose may be required.
4. Other treatment:
   - If there is carditis or severe arthritis, corticosteroid should be given (prednisolone 1 to 2 mg/kg daily).
   - If there is chorea, diazepam (for mild case) or haloperidol (in severe case) should be given.
   - If there is erythema marginatum or subcutaneous nodules, no treatment is necessary.
5. Treatment of complications like cardiac failure, valvular lesion, heart block, arrhythmia, etc. if needed.

Q. What is the **prophylactic** treatment of RF? **How long** should it be continued?

A. Recurrence is common in patient who had carditis during initial episode. In children, 20% recurrence occurs within 5 years. Recurrence is uncommon after 5 years and in patient over 25 years of age.

To prevent recurrence, oral phenoxymethylpenicillin 250 mg 12 hourly or injection benzathine penicillin 1.2 million units deep IM in the buttock every 4 weeks should be given. In penicillin-sensitive patient, erythromycin (250 mg 12 hourly) or sulfadiazine (1 g daily) may be used.

Prophylactic drug should be continued up to 21 years of age or 5 years after the last attack (recurrence after 5 years is rare), whichever comes last. After this, antibiotic prophylaxis should be given for dental or surgical procedure. However, in high-risk streptococcal infection or if the attack occurs in the 5 years or patient lives in high area of prevalence, treatment may need to be extended. If there is documented recurrence or documented rheumatic valvular heart disease, life-long prophylaxis should be considered.

Note Remember the following points:

- Skin infection with streptococci is not associated with RF. It may be associated with acute post streptococcal glomerulonephritis.
- 2 to 3% of previously healthy person may suffer from rheumatic fever following streptococcal pharyngitis.
- Streptococcal sore throat may not be present in some cases.
- More than 50% patients of RF with carditis will develop chronic valvular disease after 10 to 20 years. All the cardiac valves may be involved, but most commonly the mitral valve is affected (90%). Also aortic valve may be involved. Involvement of the tricuspid and pulmonary valves is rare.
- In chronic rheumatic heart disease, there may not be any history of rhematic fever in 50 to 60% cases.
- Arthritis is rheumatic fever recovers completely without any residual change (**Rheumatic fever licks the joints and kills the heart**). However, a rare type of arthritis called Jaccoud's arthritis is associated with deformity of metacarpophalangeal joints after repeated attack of rheumatic fever.

Q. What is the prognosis?

A. Acute attack may last up to 3 months, but recurrence may be precipitated by streptococcal infections, pregnancy, use of oral contraceptive pill, etc. 60% patients with carditis develop chronic rheumatic heat disease. Mitral valve is most commonly involved followed by aortic valve. Tricuspid and pulmonary valves are rarely involved. Usually, regurgitation of cardiac valves develops during acute attacks, while stenosis develops years later.

Q. What are the causes of migrating polyarthritis?

A. As follows:

- Rheumatic fever
- Septicemia
- Gonococcal arthritis
- Syphilitic arthritis
- Lyme arthritis
- Hyperlipidemia (type 2)
- SLE.

Q. What is the **difference** between arthritis and arthralgia?

A. Arthralgia means subjective joint pain but no swelling. Arthritis means joint pain with swelling.

EISENMENGER'S SYNDROME

CHIEF COMPLAINTS

- Breathlessness on exertion for … months
- Fatigue, weakness, dizziness for … months
- Chest pain for … months
- Cough with occasional blood stained sputum for … months.

HISTORY

History of present illness: According to the patient's statement, she has been suffering from some heart disease since her childhood. For the last … months, she is complaining of difficulty in breathing, initially which was only during moderate to severe activity, but for the last … months, she feels breathless even on mild exertion such as going to toilet, undressing, etc. There is no history suggestive of orthopnea or paroxysmal nocturnal dyspnea. Her breathlessness is not related to dust, pollen, fumes, cold, etc. and there is no diurnal or seasonal variation. She also complains of weakness, fatigue and dizziness for … months, which are gradually increasing. Occasionally, the patient experiences chest pain during moderate to severe exertion. The pain is compressive in nature, but no radiation and it is relieved by taking rest. She is also suffering from cough which is sometimes associated with mucoid sputum and streaks of blood. There is no swelling of legs or abdominal pain.

History of past illness: The patient used to feel palpitation during moderate to severe exertion. After several investigations, she was diagnosed with some heart disease. She could not mention the name of the disease (if the patient can tell the diagnosis, mention it).

Family history

Personal history

Socioeconomic history

Drug history: Mention according to the patient's statement.

GENERAL EXAMINATION

- Appearance: Ill looking, emaciated with puffy face, suffused or red conjunctiva
- Central cyanosis: Present (involving toes, fingers, lips, tongue)
- Clubbing: Present involving both toes and fingers
- There is no anemia, leukonychia, koilonychia, jaundice and dehydration
- Pulse: 104/minute, low volume
- BP: 110/70 mm Hg
- Temperature: 37°C
- Respiratory rate: 24/min
- There is no lymphadenopathy, thyromegaly.

SYSTEMIC EXAMINATION

Cardiovascular System

- Pulse: 104/minute, low volume
- BP: 110/70 mm Hg
- JVP: Raised, with prominent "a" wave.

Precordium

Inspection:

- Visible cardiac impulse in pulmonary area.

Palpation:

- Apex beat—In the left … intercostal space, … cm from midsternal line, normal in character
- Left parasternal lift—Present
- Palpable P_2—Present
- Epigastric pulsation – present.

Auscultation:

- First heart sound—normal in all the areas
- Second heart sound—louder in all the areas, P_2 is accentuated in pulmonary area
- There is a pansystolic murmur in the left 3rd and 4th intercostal space, in left parasternal area without any radiation.

Abdomen

- Liver is palpable, 2 cm from the right costal margin in right mid clavicular line. It is slightly tender, margin is sharp, surface is smooth, soft in consistency and upper border of the liver dullness is in the right fifth intercostal space, in the midclavicular line.

Other systemic examinations reveal no abnormalities.

SALIENT FEATURES

The patient Ms …, 22-year-old, student, normotensive, nondiabetic, nonsmoker, a known case of some heart disease since childhood, presented with difficulty in breathing for last … months. Initially it was only during moderate to severe activity, but for the last … months, she feels breathless even on mild exertion such as going to toilet, undressing, etc. There is no history suggestive of orthopnea or paroxysmal nocturnal dyspnea. Her breathlessness is not related to dust, pollen, fumes, cold, etc. and there is no diurnal or seasonal variation. She also complains of weakness, fatigue and dizziness for … months, which are gradually increasing. Occasionally, the patient experiences chest pain during moderate to severe exertion. The pain is compressive in nature but no radiation and it is relieved by taking rest. She is also suffering from cough which is sometimes associated with mucoid sputum and streaks of blood. There is no swelling of legs or abdominal pain. There is no family history of such illness. She used to take some medicines but could not mention the names.

On examination, general examination—mention as above.

Examination of cardiovascular system—mention as above.

Examination of other systems reveals no abnormalities.

My diagnosis is Eisenmenger's syndrome due to VSD.

Q. What are your **differential diagnoses**?

A. As follows:

- Congestive cardiac failure
- Chronic cor pulmonale.

Q. Why not CCF?

A. In CCF, the triad of engorged and pulsatile neck vein, enlarged tender liver and dependent edema should be present. It is usually secondary to other causes like mitral stenosis or left sided heart failure, which are absent in this case.

Q. Why not this is a case of chronic cor-pulmonale?

A. Cor pulmonale is defined as enlargement of right ventricle with or without failure which may be due to causes in the lung parenchyma, pulmonary vessels or chest wall (like kyphosis, scoliosis, etc.). All of these are absent in this case.

Q. What **investigations** do you suggest in this case?

A. As follows:

1. X-ray chest (enlargement of central pulmonary arteries with peripheral pruning of pulmonary vessels).
2. ECG (RVH, RAH, right axis deviation).
3. Echocardiography.

RELATED QUESTIONS AND ANSWERS

Q. What are the **clinical features** of Eisenmenger's syndrome?

A. As follows:

- Dyspnea
- Fatigue
- Syncope
- Angina
- Hemoptysis
- Features of CCF.

On examination:

- Central cyanosis (not corrected by giving 100% oxygen. Differential cyanosis (cyanosis in toes, not in the hand) occurs in PDA.
- Clubbing (differential clubbing—clubbing in toes, not in the hand, occurs in PDA).
- Pulse—low volume.
- Prominent **"a" wave in JVP.**
- Other signs of pulmonary hypertension – palpable P2, left parasternal lift, epigastric pulsation due to RVH. Ejection click and ejection systolic murmur may be present.
- TR may occur (in such case, prominent **V wave in JVP, also there may be a pansystolic murmur in left lower parasternal area).**
- Polycythemia.
- Original murmur of VSD, ASD or PDA—decrease in intensity, even may disappear.

Q. What is **Eisenmenger's syndrome**?

A. Pulmonary hypertension with reversal of shunt is called Eisenmenger's syndrome.

Causes are:

- VSD
- ASD
- PDA.

In VSD, this occurs in early life, in PDA a little later than VSD, in ASD this occurs in adult life.

In these patients, persistently raised pulmonary flow (due to left to right shunt) causes increased pulmonary resistance followed by pulmonary hypertension. This increases the pressure in right ventricle, leading to reversal of shunt (from right to left side).

Q. How to **treat Eisenmenger's syndrome?**

A. Pulmonary hypertension with reversal of shunt, when due to VSD is called Eisenmenger's complex.

Q. What is the **treatment**?

A. As follows:

- Diuretic.
- Digoxin may be given in some cases.
- Venesection may be required, especially if there is polycythemia.
- Heart lung transplantation may be done (mortality rate is very high than heart transplantation alone).

Surgery of shunt is contraindicated in Eisenmenger's syndrome, as it aggravates right sided heart failure.

Q. What are the **causes of death** in Eisenmenger's syndrome?

A. As follows:

- Right heart failure
- Infective endocarditis
- Pulmonary infarction
- Cerebral thrombosis or abscess
- Arrhythmias.

Note Remember the following points:

- If a patient has cyanosis with evidences of pulmonary hypertension, the more likely diagnosis is Eisenmenger's syndrome.
- If a patient with VSD develops Eisenmenger's syndrome, there is appearance of cyanosis, clubbing and evidences of pulmonary hypertension. However, pansystolic murmur of VSD may disappear, because of equalization of pressure between right and left ventricles.
- Patient with Eisenmenger's syndrome is at particular risk from abrupt changes in afterload that exacerbate right to left shunting (e.g. during anesthesia and also in pregnancy).

TETRALOGY OF FALLOT

CHIEF COMPLAINTS

- Breathlessness for … months
- Bluish discoloration of the lips and fingers during exertion for … months
- Weakness for … months
- Palpitation for … months
- Chest pain for … months
- Cough for … months.

HISTORY

History of present illness: According to the patient's statement, she has been suffering from breathlessness since her childhood. Her breathlessness was less marked in earlier stage, only felt during moderate to severe activity. But for the last few months, it is progressively increasing, even during mild exertion. There is no seasonal variation of breathlessness and it is not associated with exposure to dust, pollen or fume. There is no history suggestive of paroxysmal nocturnal dyspnea or orthopnea. The patient also noticed bluish discoloration of skin, finger nail, toes and lips for the last … months, which is more marked during exercise and less by taking squatting position. She also experiences diffuse chest pain, usually following any activity or after eating, which radiates to left shoulder and subsides after taking rest. She also complains of palpitation, weakness and occasional dry cough. Her bowel and bladder habits are normal. Her mother mentioned that the patient used to become bluish and breathless while feeding or crying during the first few years of life.

History of past illness

Family history

Personal history

Socioeconomic history

Drug history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient is emaciated and short in stature
- Dyspneic
- Central cyanosis (involving tongue, lips, fingers and toes) is present
- There is generalized clubbing (involving all fingers and toes)
- Pulse: 112/min, low volume, regular in rhythm and normal character
- BP: 100/60 mm Hg
- Temperature: 98ºF
- Respiratory rate: 28/min
- No anemia, leukonychia, koilonychia, edema, jaundice, lymphadenopathy or thyromegaly.

SYSTEMIC EXAMINATION

Cardiovascular System

- Pulse: 112/min, low volume, regular in rhythm and normal character
- BP: 100/60 mm Hg
- JVP: Prominent "a" wave

Precordium

Inspection:

- Visible cardiac impulse in apical and epigastric region.

Palpation:

- Apex beat—palpable in the left … intercostal space, … cm from midline, normal in character
- Left parasternal lift and epigastric pulsation—present
- Systolic thrill—present in pulmonary area.

Auscultation:

- First heart sound—normal in all the areas
- Second heart sound—P_2 is soft (or absent) in pulmonary area, A_2 is normal
- There is a harsh ejection systolic murmur in the pulmonary area, which radiates to the neck, more on inspiration.

Examination of other systems reveals normal findings.

SALIENT FEATURES

The patient Ms …, 12-year-old, student, normotensive, nondiabetic, nonsmoker, presented with breathlessness since her childhood. Her breathlessness was less marked in earlier stage, only felt during moderate to severe activity. But for the last few months, it is progressively increasing, even during mild exertion. There is no seasonal variation to this breathlessness and it is not associated with exposure to dust, pollen or fume. There is no history suggestive of paroxysmal nocturnal dyspnea or orthopnea. The patient also noticed bluish discoloration of skin, finger nail, toes and lips for the last … months, which is more marked during exercise and less by taking squatting position. She also experiences diffuse chest pain, usually following any activity or after eating, which radiates to left shoulder and subsides after taking rest. She also complains of palpitation, weakness and occasional dry cough. Her bowel and bladder habits are normal. Her mother mentioned that the patient used to become bluish and breathless while feeding or crying during the first few years of life. There is no history of such illness in her family.

On examination, general examination—mention as above.

Examination of cardiovascular system—mention as above.

Examination of other systems reveals no abnormalities.

My diagnosis is tetralogy of Fallot:

Q. Mention some **cyanotic congenital heart disease**.

A. As follows:

- Tricuspid atresia
- Transposition of great vessels
- Pulmonary atresia
- Ebstein's anomaly.

Q. What **investigations** are done in TOF?

A. As follows:

- Chest X-ray- shows boot-shaped heart, pulmonary conus is concave (small pulmonary artery), right ventricle enlarged (prominent elevated apex), oligemic lung, right-sided aortic arch in 25% cases.
- 2D echocardiography and color Doppler (diagnostic—it shows that the aorta is not continuous with the anterior ventricular septum).
- Other investigations: ECG (RVH), cardiac catheterization in some cases.

RELATED QUESTIONS AND ANSWERS

Q. What **is tetralogy of Fallot**?

A. It is a cyanotic congenital heart disease consisting of:

- Right ventricular hypertrophy.
- VSD (perimembranous, usually large, subaortic).
- Right ventricular outflow obstruction—this may be subvalvular (infundibular), valvular or supravalvular. The most common obstruction is subvalvular, either alone (50%) or in combination with pulmonary stenosis (25%).
- Overriding and dextro-position of aorta (aortic origin—2/3rd from left ventricle and 1/3rd from right ventricle).

Q. What are the **cardinal features** of TOF?

A. As follows:

- Child with growth retardation
- Clubbing
- Cyanosis
- Pulmonary ejection systolic murmur
- History of cyanotic spells during exercise (relieved by squatting).

Q. How the patient usually **presents**?

A. As follows:

- Young children usually present with cyanotic spell (Fallot's spell) during exertion, feeding or crying. They may become apneic and unconscious.
- In older children, Fallot's spells are uncommon but cyanosis becomes increasingly apparent with clubbing and polycythemia. There may be Fallot's sign.
- Shortness of breath on exertion, easy fatiguability.
- Growth retardation.
- Syncope, seizure, cerebrovascular events or even sudden death.

Q. Why **syncope** occurs in TOF?

A. During exercise, there is increased pulmonary resistance and reduced systemic vascular resistance. So, there is increased right to left shunt and admixture of blood of right and left ventricles. As a result, there is reduced cerebral oxygenation, causing syncope.

Q. Why there is **cyanosis** in TOF?

A. Because of the overriding of aorta, there is admixture of blood of right and left ventricles. Cyanosis is absent in newborn or acyanotic Fallot's.

Q. When is cyanosis **aggravated** and Why?

A. Cyanosis is aggravated during exercise and is called cyanotic spell or Fallot's spell. It is also aggravated during feeding or crying. Cyanosis is reduced by squatting. Child may be apneic and unconscious. Syncope, seizure, cerebrovascular accident (CVA) or sudden death may occur. Fallot's spell is uncommon in older children. Cyanotic spell is due to increased obstruction, as a result of increased sympathetic stimulation that occurs during exercise, feeding and crying.

Q. How **squatting** relieves cyanosis?

A. In squatting position, abdominal aorta and femoral artery are compressed. So, there is increased arterial resistance, which increases the pressure in the left ventricle, leading to diminished right to left shunt through VSD and increased flow through pulmonary artery. This reduces admixture of blood from right and left ventricles and relieves cyanosis.

Q. What are the **complications** of tetralogy of Fallot?

A. As follows:

- Infective endocarditis (common)
- Paradoxical emboli
- Cerebral abscess (10% cases)
- Polycythemia (due to hypoxemia, and may lead to cerebrovascular accident and myocardial infarction)
- Coagulation abnormality.

Q. How to **assess the severity** of TOF?

A. As follows:

- Mild case—loud and prolonged murmur
- Severe case—murmur reduced or absent.

Q. What is **pentalogy** of Fallot?

A. When TOF is associated with ASD.

Q. What is **triology** of Fallot?

A. ASD with PS with RVH.

Q. Why there is **no murmur** of VSD in TOF?

A. Because VSD is large and there is equal pressure in right and left ventricles.

Q. What is **acyanotic Fallot**?

A. When the TOF is associated with infundibular pulmonary stenosis. Outflow obstruction is mild and there is no cyanosis.

Q. How to **treat** TOF?

A. As follows:

- Surgical correction is the definitive treatment, ideally should be done prior to 5 years of age. Surgical relieve of pulmonary stenosis and closure of VSD is done.
- If pulmonary artery is hypoplastic or anatomy is unfavorable, then temporarily palliative surgery called Blalock-Taussig shunt is performed. Corrective surgery is done later on.
- Prophylactic antibiotic to prevent infective endocarditis.

Q. What is **Blalock-Taussig shunt**?

A. Blalock-Taussig shunt is the anastomosis between left subclavian artery with left pulmonary artery. This improves pulmonary blood flow and pulmonary artery development, and may facilitate definitive surgery later on.

Q. How to **treat during cyanotic spell**?

A. As follows:

- Knee-chest position of child
- High concentration of O_2
- Injection morphine or diamorphine (it relaxes right ventricular outflow obstruction)
- β-blocker may be used
- If medical therapy fails, emergency surgical shunt may be considered.

Q. What is the **prognosis** of TOF?

A. Prognosis is good after surgery, especially if operation is done in childhood. Re-stenosis, recurrence of septal defect and rhythm disorder may occur after surgery. So, regular follow-up is required in every case.

VENTRICULAR SEPTAL DEFECT (VSD)

CHIEF COMPLAINTS

- Breathlessness for … years
- Palpitation for … years.

HISTORY

History of present illness: According to the patient, she was alright … months back. Since then, she has been suffering from occasional breathlessness, more during moderate to severe exertion and relieved by taking rest. There is no history of nocturnal breathlessness or orthopnea. There is no diurnal variation of breathlessness and it is not associated with exposure to dust or cold. The patient also complains of occasional palpitation, usually with moderate to severe activity, relieved with taking rest. She does not complain of cough or hemoptysis. There is no history of chest pain, swelling of legs and syncope.

History of past illness

Family history

Personal history

Socioeconomic history

Drug history: Mention according to the statement of the patient.

GENERAL EXAMINATION

- Built: Slightly emaciated
- Anemia: Mild
- No jaundice, edema, clubbing, koilonychia, leukonychia
- No lymphadenopathy or thyromegaly
- Pulse: 84/min
- BP: 110/65 mm Hg
- Temperature: 98.8ºF.

SYSTEMIC EXAMINATION

Cardiovascular System

- Pulse: 84/minute, low volume, regular in rhythm and normal in character
- BP: 110/65 mm Hg
- JVP: Not raised.

Precordium

Inspection:

- Visible cardiac impulse in left parasternal area.

Palpation:

- Apex beat—in left ... intercostal space, ... cm from midsternal line, diffuse, thrusting in nature
- Systolic thrill is present in left parasternal area (4th or 5th intercostal area).

Auscultation:

- First and second heart sounds—normal in all the areas.
- There is a harsh pansystolic murmur in left parasternal area in 4th or 5th intercostal space (may be MDM due to increased flow through mitral valve).
- Third heart sound may be present.

Examination of other systems reveals normal findings.

SALIENT FEATURES

The patient …, 16-year-old, student, hailing from …, presented with occasional breathlessness, more during moderate to severe exertion and relieved by taking rest. There is no history of nocturnal breathlessness or orthopnea. There is no diurnal variation of breathlessness and it is not associated with exposure to dust or cold. The patient also complains of occasional palpitation, usually with moderate to severe activity, relieved with taking rest. She does not complain of cough or hemoptysis. There is no history of chest pain, swelling of legs and syncope. There is no such illness in her family. She used to take some medicine the name of which she cannot mention.

On examination, general examination—mention as above.

Examination of cardiovascular system—mention as above.

Other systems reveal no abnormalities.

My diagnosis is ventricular septal defect.

Q. Why your diagnosis is VSD?

A. Because of presence of systolic thrill and pansystolic murmur in the left lower parasternal area.

Q. What are your differential diagnoses?

A. As follows:

- Mitral regurgitation (MR)
- Tricuspid regurgitation (TR).

Q. Why not this is a case of MR?

A. In MR findings are:

- First heart sound is soft
- Pansystolic murmur in mitral area, which radiates towards the left axilla.

Q. Why not this is a case of TR?

A. In TR, findings are:

- JVP may be raised. There may be giant **V wave, oscillating up to the ear lobule.**
- First heart sound is soft in tricuspid area.
- There is a pansystolic murmur in left lower parasternal area with no radiation and the murmur is louder with inspiration.
- Also there may be enlarged, tender, pulsatile liver.

Q. Mention one single investigation to confirm your diagnosis.

A. Color Doppler echocardiogram.

Q. What **investigations** do you suggest in your case?

A. As follows:

- ECG (LVH, biventricular hypertrophy)
- X-ray chest (cardiomegaly, large pulmonary conus, large hilar arteries, plethoric lung fields)
- Echocardiography, preferably color Doppler
- Cardiac catheterization may be necessary in some cases
- CMR (cardiac magnetic resonance angiography) may be helpful.

RELATED QUESTIONS AND ANSWERS

Q. What are the **causes** of VSD?

A. As follows:

- Commonly congenital (VSD is the most common congenital heart disease)
- Acquired—rupture of interventricular septum after acute MI, rarely trauma.

Q. What is the **site** of VSD?

A. Common site is the perimembranous part of intraventricular septum (in 90% cases).

Q. Does the presentation vary with the **size of VSD**?

A. VSD may be of three types according to the size. These are:

- **Small VSD (maladie de Roger):** It is asymptomatic and usually closes spontaneously. But, there is a future risk of development of aortic regurgitation or endocarditis even after spontaneous closure. The systolic murmur is loud and prolonged.
- **Moderate VSD:** The patient presents with fatigue and dyspnea. Heart is usually enlarged with a prominent apex beat. There is often a palpable systolic thrill and a loud "tearing" pansystolic murmur at the left lower sternal edge.
- **Large VSD:** The murmur is soft. It may lead to pulmonary hypertension and Eisenmenger's complex may result.

Q. What are the **complications** of VSD?

A. As follows:

- Infective endocarditis (more common in small VSD)
- Pulmonary hypertension with reversal of shunt (Eisenmenger's syndrome)
- Heart failure.

Note

When Eisenmenger's syndrome develops, there is cyanosis, clubbing and evidence of pulmonary hypertension. Pansystolic murmur may disappear, because of equalization of pressure in right and left ventricle.

Q. What are the **causes** of plethoric lung field?

A. As follows:

- ASD
- VSD
- PDA.

(Also in congestive cardiac failure).

Q. How to **treat** VSD?

A. As follows:

- If small: Surgery is not needed; only follow-up should be done. Spontaneous closure may occur in infants if it is in the muscular part. Prophylactic penicillin for SBE may be given.
- Moderate to large: Surgical correction is needed if pulmonary to systemic flow ratio >1.5:1. Percutaneous transcatheter closure may be done.
- When Eisenmenger's syndrome develops: Surgery is contraindicated, as it aggravates right sided heart failure. Then following treatments are given:
  - Diuretic
  - Digoxin in some cases
  - Venesection, especially if there is polycythemia
  - Heart lung transplantation may be done. Mortality rate is very high than heart transplantation alone.

Note

VSD may be associated with Turner's syndrome, Down's syndrome or maternal rubella during pregnancy.

Q. Can VSD be closed **spontaneously?**

A. If small VSD, spontaneous closer may occur.

ATRIAL SEPTAL DEFECT (ASD)

CHIEF COMPLAINTS

- Weakness for ... months
- Palpitation for ... months
- Breathlessness for … months.

HISTORY

History of present illness: The patient states that she was alright … months back. Since then, she has been suffering from weakness and palpitation which are more marked on moderate to severe exertion and relieved by taking rest. She also experiences occasional breathlessness precipitated by moderate to severe exertion. However, there is no diurnal variation of this breathlessness and it is not associated with exposure to dust or fume. There is no chest pain or cough. She denies any history of swelling of legs, fever, fainting or loss of consciousness. Her appetite, bowel and bladder habits are normal.

History of past illness

Family history

Personal history

Socioeconomic history

Drug history: Mention according to the statement of the patient.

GENERAL EXAMINATION

- Appearance and built: Normal
- Anemia: Moderate
- No jaundice, edema, clubbing, koilonychia, leukonychia
- No lymphadenopathy or thyromegaly
- Pulse: 96/min
- Blood pressure: 100/65 mm Hg
- Temperature: 98.8ºF.

SYSTEMIC EXAMINATION

Cardiovascular System

- Pulse: 96/min, regular, low volume
- BP: 100/65 mm Hg
- JVP: Not raised.

Precordium

Inspection:

- Nothing significant.

Palpation:

- Apex beat—in left ... intercostal space, ... cm from midline, normal in character
- Thrill—absent.

Auscultation:

- First heart sound—normal in all the areas
- Wide and fixed splitting of 2nd heart sound
- An ejection systolic murmur is present in the left 2nd and 3rd intercostal space
- There is also a high pitched MDM in tricuspid area.

Examination of other systems reveals normal findings.

SALIENT FEATURES

Ms …, 28-year-old, service holder, normotensive, nondiabetic, nonsmoker, hailing from …, presented with generalized weakness and palpitation for … months, which are more marked on moderate to severe exertion and relieved by taking rest. She also experiences occasional breathlessness precipitated by moderate to severe exertion. However, there is no diurnal variation of this breathlessness and it is not associated with exposure to dust or fume. There is no chest pain or cough. She denies any history of swelling of legs, fever, fainting or loss of consciousness. Her appetite, bowel and bladder habits are normal. There is no history of such illness or other illness in her family. She used to take some vitamins only.

On examination, general examination—mention as above.

Examination of cardiovascular system—mention as above.

Other systems reveal no abnormalities.

My diagnosis is atrial septal defect.

Q. What are your **differential diagnoses**?

A. As follows:

- Pulmonary stenosis
- VSD.

Q. **Why not** this is a case of pulmonary stenosis?

A. In pulmonary stenosis, the findings are:

- Soft or absent P_2
- Thrill present in pulmonary area
- Wide and fixed splitting of 2nd heart sound is absent
- ESM may radiate to the neck.

Q. **Why not** this is a case of VSD?

A. In VSD, the findings are:

- Systolic thrill in the left lower parasternal area
- Pansystolic murmur in the left lower parasternal area.

Q. What **investigations** do you suggest in ASD?

A. As follows:

- X-ray chest—cardiomegaly (right ventricle and right atrium are enlarged, also small left artium and normal aorta), large pulmonary conus, large hilar arteries and plethoric lung fields (lung fields become oligemic, when pulmonary hypertension develops).

- ECG.
- 2D echocardiography and color Doppler (transesophageal echocardiography is better).
- Cardiac catheterization in some cases (fluoroscopy shows hilar dance).
- MRI (or CMR) may be helpful.

RELATED QUESTIONS AND ANSWERS

Q. What is **wide and fixed splitting** of 2nd sound and why wide and fixed splitting?

A. Wide and fixed splitting means it is remaining same in inspiration and expiration.

- Wide—because of delay in right ventricular ejection, which is due to increased stroke volume.
- Fixed—because of equalization of pressure between left and right atrium, so no change of 2nd heart sound with respiration (normally, there is wide splitting during inspiration due to delay of closure of pulmonary valve).

Q. What are the **murmurs** in ASD?

A. Two murmurs:

- ESM—due to increased flow through pulmonary valve.
- MDM—due to increased flow through tricuspid valve.

(No murmur due to ASD, because of equal pressure between left and right atrium).

Q. What are the **types** of ASD?

A. Two types:

- Ostium primum (15% cases)—results from atrioventricular defect in septum and there is involvement of AV valve, so there may be MR or TR.
- Ostium secundum (75% cases)—defect mainly at the fossa ovalis in the atrial mid septum (it should not be confused with patent foramen ovale, which is a normal variant, not a true septal defect. PFO is usually asymptomatic, but may be associated with paradoxical emboli and increased incidence of embolic stroke. PFO may be treated with angiographic closure using transcatheter clamshell device to prevent thromboembolism).

(ASD is common in female, M:F = 1:2. Ostium primum may occur in Down's syndrome).

Q. What is the **ECG finding** in ASD?

A. ECG shows:

- In primum type—RBBB with left axis deviation.
- In secundum type—RBBB with right axis deviation.

Q. What are the **complications** of ASD?

A. As follows:

- Pulmonary hypertension with reversal of shunt (Eisenmenger's syndrome).
- Arrhythmia—atrial fibrillation (the most common).
- Embolism (pulmonary and systemic) and brain abscess.

Q. What are the findings when there is **reversal of shunt**?

A. As follows:

- Both murmurs are reduced in intensity
- P_2 is loud
- Systolic ejection sound is accentuated
- Other features of pulmonary hypertension are found.

Q. What is **Lutembacher's** syndrome?

A. ASD with an acquired rheumatic mitral stenosis.

Q. How to **treat** ASD?

A. As follows:

- Small ASD—Surgery is not needed, only follow-up should be done (the patient usually lives a normal life).
- Moderate to large—Surgical closure should be done, if pulmonary flow to systemic flow is 2:1 or more.
- Angiographic closure is possible with transcatheter clamshell device.
- If Eisenmenger's syndrome develops—surgical closer is contraindicated (For other treatment, see in Eisenmenger's syndrome).

PATENT DUCTUS ARTERIOSUS (PDA)

CHIEF COMPLAINTS

- Breathlessness for … months
- Palpitation for ... months
- Weakness and loss of appetite for ... months.

HISTORY

History of present illness: The patient was quite well ... months back. Since then, he has been suffering from occasional breathlessness, more during moderate to severe exertion and relieved by taking rest. There is no history of PND or orthopnea. There is no seasonal variation and it is not related to intake of any food or exposure to dust, fume, pollen, etc. The patient also complains of occasional palpitation, usually with moderate to severe activity or during anxiety. He also experiences weakness and loss of appetite. His bowel and bladder habits are normal. He does not complain of cough, hemoptysis, chest pain or fever.

History of past illness

Family history

Personal history

Socioeconomic history

Drug history: Mention according to the statement of the patient.

GENERAL EXAMINATION

- Appearance: Normal
- Anemia: Mild
- No jaundice, edema, clubbing, koilonychia, leukonychia
- No lymphadenopathy or thyromegaly
- Pulse: 88/min
- BP: 120/60 mm Hg
- Temperature: 98.8ºF.

SYSTEMIC EXAMINATION

Cardiovascular System

- Pulse: 88/minute, high volume (bounding), regular in rhythm, no radio-femoral or radio-radial delay
- BP: 120/60 mm Hg
- JVP: Not raised.

Precordium

Inspection:

- Visible cardiac impulse in apical area and another impulse in pulmonary area.

Palpation:

- Apex beat—in left ... intercostal space, ... cm from midline, thrusting or heaving in nature
- Systolic thrill—present in pulmonary area (may be diastolic also)
- Pulmonary arterial pulsation may be felt.

Auscultation:

- First and second heart sounds—normal in all the areas (may be reverse splitting of 2nd heart sound, if large shunt).
- There is a continuous murmur in left 2nd and 3rd intercostal space, more prominent in systole (murmur is prominent on expiration, may be heard posteriorly), radiates to the neck.
- There may be MDM (due to increased flow).

Examination of other systems reveals normal findings.

SALIENT FEATURES

The patient, ..., 16-year-old, student, hailing from ..., presented with occasional breathlessness for … months which is more during moderate to severe exertion and relieved by taking rest. There is no history of PND or orthopnea. There is no seasonal variation and it is not related to intake of any food or exposure to dust, fume, pollen, etc. The patient also complains of occasional palpitation, usually with moderate to severe activity or during anxiety. He also experiences weakness and loss of appetite. His bowel and bladder habits are normal. He does not complain of cough, hemoptysis, chest pain or fever. There is no family history of such illness. He used to take some medicines but could not mention the names.

On examination, general examination—mention as above.

Examination of cardiovascular system—mention as above.

Other systems reveal no abnormalities.

My diagnosis is patent ductus arteriosus.

Q. What are your **differential diagnoses**?

A. The typical continuous murmur is highly suggestive of PDA. However, any cause of continuous murmur should be excluded such as:

- Arteriovenous fistula (coronary, pulmonary or systemic)
- Venous hum
- Rupture of sinus of Valsalva to the right ventricle or atrium.

Q. What is **venous hum?**

A. It is a continuous murmur, due to kinking and partial obstruction of one of the large veins in the neck. It is found in the neck above the clavicle and upper part of chest, more on the right side of sternum. The hum can be obliterated by pressure on the neck or lying down or altering the position of neck (as there is reduction of venous obstruction). It is accentuated by sitting with head extended and turned to the side opposite to that auscultated. Venous hum has no clinical significance, commonly present in children, should not be confused with any pathology.

Q. What **investigations** do you suggest in PDA?

A. As follows:

- ECG: It may be normal. There may be LVH, but RVH occurs in Eisenmenger's syndrome.
- X-ray chest: Cardiomegaly (left ventricle and left atrium are enlarged, large aorta), large pulmonary conus, large hilar arteries, plethoric lung fields.

- 2D echocardiography and color Doppler echocardiography.
- MRI or CMR (cardiac magnetic resonance angiography) may be helpful.
- Cardiac catheterization may be necessary in some cases.

RELATED QUESTIONS AND ANSWERS

Q. What is the **murmur** in PDA?

A. Continuous murmur (machinery murmur like train in a tunnel), with late systolic accentuation.

Q. What are the **causes** of continuous murmur?

A. As follows:

- PDA
- Arteriovenous fistula (coronary, pulmonary or systemic)
- Aortopulmonary fistula (may be congenital or Blalock-Taussig shunt)
- Venous hum
- Rupture of sinus of Valsalva to the right ventricle or atrium.

Q. What are the **causes** of PDA?

A. Common in female, M:F = 1:3. Probable etiological factors are:

- Maternal rubella in the first trimester
- Birth at high altitude with continuous prenatal hypoxia
- Prematurity.

Note

During fetal life, ductus arteriosus connects pulmonary artery at its bifurcation to the descending aorta just below the origin of left subclavian artery and permits blood flow from pulmonary artery to aorta. After birth, within hours or days, it closes spontaneously and remains as ligamentum arteriosum.

In PDA, it allows blood to flow from aorta to pulmonary artery. Up to 50% of left ventricular output may enter into pulmonary artery, because pressure in aorta is higher.

Q. What are the **findings** in reversal of shunt?

A. As follows:

- Cyanosis and clubbing in lower limb, absent in upper limb (called differential cyanosis and differential clubbing).
- Murmur—quiet or absent or systolic only (diastolic disappears).
- Evidence of pulmonary hypertension.

Q. What are the **complications** of PDA?

A. As follows:

- Pulmonary hypertension with reversal of shunt (Eisenmenger's syndrome)
- CCF
- Infective endocarditis
- Arrhythmia (atrial fibrillation)
- Duct may rupture or calcify.

Q. How to **treat** PDA?

A. As follows:

- Majority of PDA are small and can be closed at cardiac catheterization by using implantable occlusive device.

- In large PDA, surgical closure should be done as early as possible.
- Prophylaxis for infective endocarditis.
- In neonate (1 to 3 weeks old), indomethacin (0.2 mg/kg IV) or ibuprofen may be given to constrict and close PDA by inhibiting prostaglandin E synthesis (prior to birth, the duct is kept patent by the effect of circulating prostaglandin). It is not helpful in older children.
- If Eisenmenger's syndrome develops, surgery is contraindicated (see Eisenmenger's syndrome).

Prognosis: If untreated, 1/3rd individuals die from heart failure, pulmonary hypertension or endocarditis by the age of 40 and 2/3rd by the age of 60.

COARCTATION OF AORTA

CHIEF COMPLAINTS

- Frequent headache, dizziness and giddiness for … years
- Cramps in the legs for … years
- Palpitation for … years.

HISTORY

History of present illness: The patient was well and fit ... months back. Since then, he has been suffering from frequent headache, dizziness and giddiness. Headache is diffuse, more marked over the forehead, throbbing in nature, not associated with nausea or vomiting and relieved by taking high dose paracetamol or after sleep. He also complains of cramping in both lower limbs for the same duration during physical activity or walking, which is relieved by taking rest or massaging. The patient also experiences occasional palpitation, even with mild exertion and subsides with rest. There is no history of loss of consciousness, chest pain, cough or any bleeding manifestations.

History of past illness

Family history

Personal history

Socioeconomic history

Drug history: Mention according to the statement of the patient.

GENERAL EXAMINATION

- Appearance: Normal
- Anemia: Mild
- No jaundice, edema, clubbing, koilonychia, leukonychia
- No lymphadenopathy or thyromegaly
- Pulse: 80/min
- BP: 160/90 mm Hg in both arms. In the lower limbs, it could not be recorded. (Usually large sphygmomanometer calf is required to detect pressure in the lower limb)
- Temperature: 98.8ºF.

SYSTEMIC EXAMINATION

Cardiovascular System

- Pulse: 80/minute, normal in rhythm, high volume in upper limb, femoral pulse is very feeble. There is radio-femoral delay, but no radio-radial delay.
- BP: 160/90 mm Hg in both arms. In the lower limbs it could not be recorded.
- JVP: Not raised.
- Carotid pulse: High volume and vigorous.
- There is visible suprasternal, right carotid pulse and supraclavicular pulsation.

Precordium

Inspection:

- Visible cardiac impulse
- Visible dilated tortuous artery around the scapula, anterior axilla and over the left sternal border (collateral vessels are best seen by sitting and bending forward, with arm hanging by the side).

Palpation:

- Apex beat—in left ... intercostal space, heaving in nature
- (There may be thrill over the collateral vessels).

Auscultation:

- Both first and second heart sounds – normal
- Murmur—systolic murmur audible in, ... intercostal space close to the sternum and better heard in 4th intercostal space posteriorly (site of coarctation). May be ejection click, ESM in aortic area and EDM (bicuspid aortic valve or dilatation of aortic valve due to aneurysm, causing AR).

Examination of other systems reveals normal findings.

SALIENT FEATURES

The patient, Mr ..., 26-year-old, student, nonsmoker, nondiabetic presented with frequent headache, dizziness and giddiness for … years. Headache is diffuse, more marked over the forehead, throbbing in nature, not associated with nausea or vomiting and relieved by taking high dose paracetamol or after sleep. He also complains of cramping in both lower limbs for the same duration during physical activity or walking which is relieved by taking rest or massaging. The patient also experiences occasional palpitation, even with mild exertion and subsides with rest. There is no history of loss of consciousness, chest pain, cough or any bleeding manifestations. There is no family history of such illness. He used to take some vitamins only.

On examination, general examination—mention as above.

Examination of cardiovascular system—mention as above.

Other systems reveal no abnormalities.

My diagnosis is hypertension due to coarctation of aorta.

Q. Why is it a case of coarctation of aorta?

A. Because radial pulse is high volume, femoral pulse is feeble and there is radio-femoral delay. Also, the BP is very high in upper limbs and very low in lower limbs.

Q. What **investigations** do you suggest in coarctation of aorta?

A. As follows:

1. X-ray chest P/A view:
   - Poorly developed aortic knuckle (or elongated aortic knuckle), cardiomegaly, post-stenotic dilatation of aorta.
   - Rib notching, mostly at the middle part posteriorly, due to enlargement of intercostal arteries from 3rd rib downwards (1st and 2nd ribs are not affected, because intercostal arteries here arise from subclavian artery above the constriction).
   - Figure of **3** (constriction at coarctation, prestenotic and poststenotic dilatation).

2. ECG (LVH).
3. Others: CT scan and CMR (cardiac magnetic resonance angiography) are ideal for confirming the diagnosis. Echocardiogram and aortography may also be done.

RELATED QUESTIONS AND ANSWERS

Q. Why **murmur** in coarctation of aorta?

A. Usually due to increased flow through collateral vessels, also may be due to associated congenital bicuspid aortic valve.

Q. What are the **types** of coarctation of aorta?

A. 2 types:

- Post-ductal (adult type): Commonly below the origin of left subclavian artery, where ductus arteriosus joins the aorta.
- Pre-ductal (infantile type, 2%): Above the origin of left subclavian artery. So, left radial pulse is weak and rib notching on right side. Without other communication, patients do not survive. It may be associated with PDA.

Q. What **type of hypertension** develops and why?

A. Usually systolic hypertension, diastolic may be normal. Causes of hypertension are:

- Mechanical
- Renin angiotensin mechanism (due to coarctation, there is less blood flow to kidney)
- Resetting of baroreceptors.

Note

Collateral vessels are formed involving periscapular, internal mammary and intercostal arteries.

Q. What is **reverse coarctation?**

A. When pulse is absent in upper limb, but present in lower limb, it is called reverse coarctation. It occurs in Takayasu's disease.

Q. What are the **complications** of coarctation of aorta?

A. As follows :

- Hypertension and its complication (LVF, CVA)
- Infective endocarditis
- Rupture at the coarctation site
- Dissecting aneurysm
- Aneurysm of aorta
- Subarachnoid hemorrhage (rupture of Berry aneurysm of circle of Willis).

Q. What are the **causes of death** in coarctation of aorta?

A. As follows:

- Acute left ventricular failure
- Dissecting aneurysm or aorta
- Subarachnoid hemorrhage (due to rupture of aneurysm of circle of Willis)
- Cerebral hemorrhage.

Associations in coarctation of aorta:

- Bicuspid aortic valve (in 50% cases)

- VSD
- PDA
- Aneurysm of circle of Willis (5 to 10% cases)
- In female, Turner's syndrome
- Occasionally, Marfan's syndrome.

Note Remember the following points:

- Coarctation of aorta is twice more common in male than female
- It is 7% of all congenital heart diseases
- Even if there is hypertension, renal involvement is unusual and the fundal changes are also unusual.

Q. What are the **causes** of coarctation?

A. As follows:

- Congenital (the most common).
- Rarely, may be acquired in trauma, Takayasu's disease.

Q. What are the **presentations** of coarctation of aorta?

A. As follows:

- May be asymptomatic
- Symptoms such as headache, nose bleeding, claudication of lower limbs and cold legs (due to poor blood flow in lower limbs).

Q. What are the **sites** of collaterals?

A. Severe narrowing of the aorta encourages the formation of collateral arterial circulation involving the pericapsular, internal mammary and intercostals arteries, may result in localized bruit.

Q. What are the **causes** of unilateral rib notching?

A. As follows:

- Coarctation of aorta (before the origin of left subclavian artery)
- Blalock-Taussig shunt (iatrogenic, done in Fallot's tetralogy)
- Subclavian artery obstruction
- Neurofibromatosis
- Congenital.

Q. What are the causes of **bilateral rib notching**?

A. Usual causes are:

- Coarctation of aorta (after the origin of left subclavian artery)
- Neurofibromatosis
- Congenital.

Q. What are the causes of **rib notching**?

A. As follows:

1. Arterial cause:
   - Coarctation of aorta
   - Subclavian artery obstruction.
2. Venous causes:
   - SVC obstruction (rare)
   - IVC obstruction (rare).

3. Neurological cause:
   - Neurofibromatosis
   - Enlarged nerve (as in amyloidosis, congenital hypertrophic polyneuropathy).
4. Others:
   - Congenital
   - Blalock-Taussig shunt (iatrogenic).

Q. What is the **treatment** of coarctation of aorta?

A. As follows:

- Coarctation of aorta should be treated surgically as early as possible, preferably before 5 years of age. Surgical resection and end-to-end anastomosis is usually done. If coarctation is extensive, then prosthetic vascular graft may be done (if surgery is done during adolescence or adulthood, hypertension may persist in up to 70% cases, because of irreversible changes in arterioles or renal damage. If done in early childhood, hypertension usually resolves completely.)
- Balloon angioplasty may be helpful. It is particularly effective after restenosis.

Prognosis after surgery:

- If surgical correction is done in childhood, there is 25-year survival in 83%. If surgery is delayed until adulthood, 25-year survival rate drops to 75%. Without surgery, only 25% live up to 50 years of age, while cardiac failure occurs in 2/3rd of surviving patients over 40.
- In few cases, there is restenosis as the child grows. This can be treated by balloon angioplasty.
- If operation is delayed, patient may have persistent hypertension, because of irreversible changes in the arterioles.
- May develop paradoxical hypertension, due to baroreceptor induced increased sympathetic activity (detected by increased serum and urinary catecholamines).
- Coexistent bicuspid aortic valve, which occurs in over 50% of cases, may lead to progressive aortic stenosis or regurgitation, and also requires long-term follow-up.

HYPERTROPHIC CARDIOMYOPATHY

CHIEF COMPLAINTS

- Shortness of breath on exertion for … months
- Palpitation for … months
- Chest pain for … months.

HISTORY

History of present illness: The patient was quite well … months back. Since then, he has been suffering from shortness of breath, palpitation and chest pain on moderate to severe exertion and relieved by rest. The pain is central, compressive in nature but there is no radiation. There is no history of dizziness, loss of consciousness, vertigo, cough, paroxysmal nocturnal dyspnea, orthopnea. His bowel and bladder habits are normal.

History of past illness: There is no history of rheumatic fever or other illnesses.

Family history: One of his brother suddenly died at the age of 30. All other members are in good health.

Personal history

Socioeconomic history

Drug history

Psychiatric history: Mention according to the patient's history.

GENERAL EXAMINATION

As in other valvular diseases, mention according to your findings.

SYSTEMIC EXAMINATION

Cardiovascular System

- Pulse: 88/min, normal volume, normal in rhythm, no radiofemoral or radioradial delay
- Carotid pulse: Jerky
- JVP: Normal
- BP: 95/80 mm Hg (low systolic, normal diastolic and narrow pulse pressure).

Precordium

Inspection:

- No abnormality.

Palpation:

- Apex beat—in the left … intercostal space ... cm from midline, heaving in nature (may be double apical impulse).
- A systolic thrill may be palpable at apex from severe mitral regurgitation or at the lower left sternal border from outflow tract obstruction.

Auscultation:

- First and second heart sounds—normal in all the areas.
- Fourth heart sound may be present (due to atrial contraction).
- There is a harsh ejection systolic murmur at the left lower sternal border (increasing during standing and Valsalva maneuver and decreases during squatting or sustained hand grip). There may be pansystolic murmur at the apex due to mitral regurgitation.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, a 28-year-old cultivator, smoker, nondiabetic, non-hypertensive, presented with shortness of breath, palpitation and chest pain on moderate to severe exertion and relieved by rest for the last … months. The pain is central, compressive in nature but there is no radiation. There is no history of dizziness, loss of consciousness, vertigo, cough, paroxysmal nocturnal dyspnea, orthopnea. His bowel and bladder habits are normal. There is no history of rheumatic fever or other illnesses. One of his brothers suddenly died at the age of 30 without any history of previous illness. All other members are in good health.

On examination, general examination—nothing significant.

Examination of cardiovascular system—mention as above.

Other systems revealed no abnormalities.

With these findings, I have some **differential diagnoses:**

- Mitral regurgitation
- Aortic stenosis
- Hypertrophic cardiomyopathy.

Q. Why not pulmonary stenosis?

A. In pulmonary stenosis, findings are:

- Systolic thrill in pulmonary area.
- Left parasternal lift and epigastric pulsation may be present (due to RVH).
- P_2 is soft, A_2 is normal (wide splitting of the second heart sound may be present).
- Ejection systolic murmur in pulmonary area, which radiates to the left side of neck (murmur is more on inspiration).
- Apex is normal (not heaving as in AS).

Q. Why not AS?

A. In AS, the findings are:

- Pulse is low volume and slow rising.
- BP shows low systolic, normal diastolic and narrow pulse pressure.
- Systolic thrill in aortic area.
- Second heart sound shows soft A_2 in all the areas, P_2 is normal, may be reversed splitting of 2nd heart sound.
- There is a harsh ejection systolic murmur in aortic area which radiates towards the neck.

Q. What investigations should be done?

A. As follows:

- X-ray chest (may be normal)
- ECG (may be LVH, infarct, deep T-bizarre pattern)

- Echocardiogram (diagnostic)
- Cardiac MR
- Genetic analysis.

RELATED QUESTIONS AND ANSWERS

Q. What is **cardiomyopathy?** What are the **types**?

A. Cardiomyopathies are a group of disease that primarily affect the heart muscle and not due to the result of congenital, acquired valvular, hypertension, coronary arterial or pericardial abnormalities.

It is of 3 types:

- Dilated cardiomyopathy (ischemic)
- Hypertrophic cardiomyopathy
- Restrictive cardiomyopathy.

Q. What is **hypertrophic cardiomyopathy** (HCM)?

A. Hypertrophic cardiomyopathy (HCM) is a disease of the heart muscle characterized by hypertrophy of cardiac muscle with misalignment of the cardiac fibers. Hypertrophy may be generalized or localized to the interventricular septum (asymmetrical septal hypertrophy) or other regions (apical hypertrophic cardiomyopathy).

Note Remember the following points:

- It is a common type of cardiomyopathy. Prevalence is 1:500 to 1:1000, inherited as autosomal dominant.
- About half of the patients have a positive family history. First degree relatives should be screened.
- Previously it was called hypertrophic obstructive cardiomyopathy (HOCM), but left ventricular outflow obstruction is found only in 1/3rd patients.

Q. What are the **types** of HCM?

A. As follows:

- Asymmetrical septal hypertrophy (70%)
- Basal septal hypeatrophy (15 to 20%)
- Concentric (8 to 10%)
- Apical or lateral wall (< 2%).

Q. What are the **presentations** of HCM?

A. As follows:

- Angina on effort
- Dyspnea on effort
- Presyncope or syncope on effort
- Sudden death.

Q. How to **treat** HCM?

A. As follows:

1. Specific measures:
   - β-blocker, rate limiting calcium channel blocker (verapamil, diltiazem) and disopyramide for symptomatic relief and prevention of syncope.
   - Amiodarone may be helpful in arrhythmia.

- In some patients with significant left ventricular outflow obstruction and symptoms, dual chamber pacing may be needed.
- Outflow tract obstruction can be improved by partial surgical resection (myectomy) or by iatrogenic infarction of the basal septum (septal ablation), by a catheter delivered alcohol solution.
- ICD should be considered in patient with clinical risk factors for sudden death.
- Cardiac transplantation may be needed in CHF not responding to treatment.
- Infective endocarditis prophylaxis may be needed.

2. Advice:
   - Vigorous exercise and dehydration should be avoided.

Q. What are the **risk factors** for sudden death in HCM?

A. As follows:
- A history of previous cardiac arrest or sustained VT
- Recurrent syncope
- An adverse genotype and/or family history of sudden cardiac death (< 50 years old)
- Failure of blood pressure to rise during exercise (no change or hypotension)
- Non-sustained VT on 24 hour Holter monitoring
- Marked increase in left ventricular wall thickness (> 30 mm on echocardiography)
- Delayed gadolinium enhancement on cardiac MRI.

Q. What drugs should be **avoided**?

A. As follows:
- Digoxin
- Vasodilators
- Diuretics
- Nitrates
- Dihydropyridine calcium channel blockers
- Alcohol (may cause vasodilatation).

Q. What is the effect of HCM in **pregnancy**? What **precautions** should be taken?

A. HCM is not a contraindication to pregnancy. The patient usually tolerates pregnancy well if not severely symptomatic prior to conception. There is no evidence that pregnancy increases the risk of sudden cardiac death (SCD). Following precautions should be taken:
- Prenatal counseling regarding risk of disease in offspring
- The patient should have regular follow-up in well-equipped center with expertise in high-risk pregnancies and cardiac disease
- β-blockers or calcium blockers should be continued.

CHAPTER 4

Gastroenterology

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CHRONIC DUODENAL ULCER

CHIEF COMPLAINTS

- Pain in the epigastric region for … months
- Heart burn, nausea and belching for … months.

HISTORY

History of present illness: The patient states that he was quite well … months back. Since then, he has been suffering from frequent pain in the epigastric region. The pain is burning or dull aching in nature, more marked in empty stomach, like hunger pain. It is relieved by taking food or antacid. Sometimes, the pain appears at the late hours of night, awakening the patient from sleep, relieved by taking food or antacid. The patient also complains of occasional nausea and belching for … months. There is no history of vomiting, hematemesis, melena, anorexia, weight loss or weakness. His bowel and bladder habits are normal.

History of past illness: Nothing significant.

Family history: His parents are alive and in good health. His wife and two children are good health. There is no history of similar illness in his family.

Personal history: He is a government service holder. He smokes about 20 to 30 sticks of cigarettes per day for the last 25 years. There is no history of taking alcohol.

Socioeconomic history: He comes from a middle class family and lives in a brick built house with good sanitation and water supply.

Drug history: He occasionally takes antacids, ranitidine and omeprazole for his illness. However, there is no history of taking any NSAIDs or steroid.

GENERAL EXAMINATION

- The patient appears to be in good health
- No anemia, jaundice, clubbing, cyanosis, koilonychia, leukonychia or oedema
- No lymphadenopathy or thyromegaly
- Pulse: 80/min
- BP: 120/80 mm Hg.

SYSTEMIC EXAMINATION

Gastrointestinal System

Lips, gums, teeth, tongue and oral cavity—normal.

Abdomen:

Inspection: Normal

Palpation:

- Tenderness in epigastric region, no palpable mass
- Liver: Not palpable
- Spleen: Not palpable

- Kidneys: Not ballotable
- No lump or mass.
- Genetalia: Normal.

Percussion:

- Percussion note is tympanitic
- No shifting dullness.

Auscultation:

- Bowel sounds—normal.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, a 42-year-old, serviceman, normotensive, nondiabetic, smoker, used to take 20 to 30 sticks per day, hailing from …, presented with frequent pain in the epigastric region for ... months. The pain is burning or dull aching in nature, more marked in empty stomach, like hunger pain. It is relieved by taking food or antacid. Sometimes, the pain appears at the late hours of night, awakening the patient from sleep, relieved by taking food or antacid. The patient also complains of occasional nausea and belching for … months. There is no history of vomiting, hematemesis, melena, anorexia, weight loss or weakness. His bowel and bladder habits are normal. He occasionally takes antacids, ranitidine and omeprazole for his illness. However, there is no history of taking NSAID or steroid. There is no similar illness in his family.

On examination—general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is chronic duodenal ulcer.

Q. What are your **differential diagnoses**?

A. As follows:

- Chronic cholecystitis
- Chronic pancreatitis
- Non-ulcer dyspepsia
- Gastroesophageal reflux disease
- Irritable bowel syndrome.

Q. How to **confirm** your diagnosis?

A. Endoscopy of upper GIT.

Q. What **investigations** do you suggest?

A. As follows:

- Endoscopy of the upper GIT.
- If the patient refuses endoscopy or cannot be done due to poor general condition, recent MI or unstable angina—barium meal X-ray of stomach and duodenum should be done.
- USG of the whole abdomen to exclude other causes.
- Screening for *Helicobacter pylori* (see below).
- To exclude other causes—stool microscopy for ova, trophozoites, occult blood test.

RELATED QUESTIONS AND ANSWERS

Q. What are the **sites** of peptic ulcer disease?

A. As follows:

- First part of duodenum

- Around lesser curvature of stomach
- Lower end f oesophagus
- In gastrojejunostomy stoma
- Rarely, in Meckel's diverticulum.

Q. What is the **etiology or risk factors** for PUD?

A. As follows:

- *H. pylori* infection
- Drugs—aspirin or other NSAIDs, steroid, KCl, bisphosphonate
- Smoking
- Others—acid hypersecretory disorder (e.g. Zollinger Elison syndrome), hyperparathyroidism, Crohn's disease, sarcoidosis, myeloproliferative disorder.

Q. What is ***Helicobacter pylori***?

A. *H. pylori* is a spiral shaped Gram negative multiple, flagellete bacterium. It is slowly growing and produces urease. It colonizes in the mucosal layer of the gastric antrum, also found in duodenum only in areas of gastric metaplasia. Its prevalence is high in developing countries (80 to 90%) and low in developed countries (20 to 50%).

Mode of transmission: It spreads from person to person by feco-oral or oro-oral, either by kissing or ingestion of contaminated vomit. Infection is acquired in childhood, persist for life unless treated. Majority of the infected case remain healthy and asymptomatic, only few develop clinical disease, especially in smokers.

Q. How *H. pylori* causes PUD?

A. It is associated with 90% duodenal ulcers and 70% gastric ulcers. After infection, *H. pylori* causes the following:

1. Antral gastritis: Usual effect of *H. pylori* infection, commonly asymptomatic but may cause dyspepsia. After antral gastritis, excess gastrin release from antral G cells, which causes hypergastrinemia that increases acid output.
2. Duodenal ulcer (DU): *H. pylori* increases acid secretion due to excess gastrin secretion and also increased parietal cell mass. *H. pylori* induced gastritis causes depletion of somatostatin from D cells, which leads to loss of negative feedback on gastrin secretion, resulting in excess acid secretion. In addition, duodenal bicarbonate secretion is decreased by *H. pylori* inflammation. There is also gastric metaplasia in which *H. pylori* colonizes, causing local release of cytokines that cause further damage.
3. Gastric ulcer (GU): It is associated with gastritis affecting the body and antrum of the stomach. This leads to gastric atrophy, parietal cell loss and reduced acid production (hypochlorhydria). Reduction of gastric mucosal resistance due to cytokine production by the infection or due to alteration in gastric mucosa causes gastric ulcer. However, most of the gastric ulcers are probably due to combination of *H. pylori* infection, NSAIDs and smoking.

Q. How to **diagnose** *H. pylori* infection?

A. As follows:

1. Non invasive tests:
   - Serology—anti *H. pylori* antibody (IgG), 90% sensitive, 83% specific.
   - ^{13}C urea breath test—measurement of $^{13}CO_2$ in the breath after ingestion of ^{13}C urea it is 97% sensitive and 96% specific. False negative result may occur if the patient is taking PPI. This test can be done by using a rapid release tablet (positive in 15 minutes).

- Fecal antigen test—97.6% sensitive, 96% specific. This test is useful in the diagnosis and for monitoring the efficacy of eradication. The patient should stop taking PPI for one week before the test, but can continue H_2 blocker.

2. Invasive tests (antral biopsy by endoscopy) –
   - Rapid urease tests, e.g. CLO, Pyloritek (its specificity is 95% and sensitivity is 85%).
   - Histology (modified Giemsa stain of gastric biopsy specimen)—*H. pylori* can be detected from the gastric mucosa.
   - Microbiological culture (biopsy material in a special media)—it is slow, less sensitive.

Q. What are the **indications** of *H. pylori* eradication?

A. As follows:

- All patients with proven gastric or duodenal ulcer
- *H. pylori* positive dyspepsia
- MALToma
- Atrophic gastritis
- After gastric cancer resection
- First degree relatives of patients with gastric cancer.
- *H. pylori* infection should be sought for and treatment in unexplained iron deficiency anemia, ITP.

Note Remember the following:

In asymptomatic case with *H. pylori* infection, there is controversy. Treatment may be considered with the hope that symptoms will be reduced, and also, to prevent gastric cancer.

Q. How to **treat *H. pylori*** infection?

A. As follows:

1. First-line therapy: The following combination is given for **7 days**.
   - Omeprazole 20 mg 12 hourly PLUS
   - Clarithromycin 500 mg 12 hourly PLUS
   - Amoxicillin 1 g 12 hourly or Metronidazole 400 mg 12 hourly.
2. Second-line therapy: Given if there is failure of first line therapy. The following combination is given for **14 days**—
   - PPI 20 to 40 mg 12 hourly PLUS
   - Bismuth citrate 120 mg 6 hourly PLUS
   - Metronidazole 400 mg 8 hourly PLUS
   - Tetracycline 500 mg 6 hourly.

Note Remember the following points:

- None of the drugs is effective alone. So, 2 powerful antibiotics and powerful acid suppressive drugs are given.
- Success rate is 90%.
- Reinfection is uncommon in developed countries (1%), but it is more in developing countries.
- Sequential therapy is used in areas where the resistance is high.

Q. What are **complications** of chronic duodenal ulcer?

A. As follows:

- Acute—bleeding (leading to hematemesis and melena), perforation
- Chronic—gastric outlet obstruction (pyloric stenosis), hourglass contracture, tea-pot diformity. (Carcinoma stomach occur in gastric ulcer, never in duodenal ulcer).

Q. How will you **manage** a case of chronic duodenal ulcer?

A. As follows:

Aims of management:

- To relieve symptoms
- To induce healing
- To prevent recurrence
- To prevent future complication.

Treatment:

1. *H. pylori* eradication (see above).
2. General measures:
   - Avoid smoking, aspirin and NSAIDs (moderate alcohol is not harmful).
   - No special dietary advice.
3. Other treatments like antacid, H_2 antagonist, PPIs, chelates, complex salts (sucralfate), prostaglandin analogs may be given for short-term therapy.
4. Maintenance treatment may be needed in some cases.
5. Surgical treatment: Less needed nowadays. Indications are:
   - Emergency:
     - Perforation
     - Hemorrhage
   - Elective:
     - Complications, such as pyloric stenosis
     - Recurrent ulcer following gastric surgery.

Gastrojejunostomy with vagotomy is usually done. Sometimes partial gastrectomy may be done.

Q. How to **manage peptic ulcer bleeding?**

A. The patient should be assessed and managed simultaneously in the following way:

1. IV access should be established. Resuscitation is done by IV normal saline (crystalloid) or colloid solution.
2. Initial clinical assessment:
   - To check circulatory status—see pulse and BP, urine output, other features of shock like cold clammy extremities. CVP should be monitored in patient with severe bleeding, particularly if the patient has cardiac disease.
   - Other systems—cardiorespiratory, cerebrovascular or renal diseases should be assessed.
   - Evidence of liver disease should be sought.
3. Blood tests:
   - Blood grouping and cross matching
   - Full blood count
   - Urea and electrolytes
   - Liver function tests
   - Prothrombin time.
4. Blood transfusion should be given when the hemoglobin is less than 10 g/dL or the patient is in shock. CVP is monitored and fluid replacement should be adjusted accordingly.
5. Oxygen should be given to all patients in shock (pallor, cold nose, systolic BP < 100 mm Hg, pulse > 100/min).
6. Intravenous PPI therapy (omeprazole 80 mg followed by infusion 8 mg/h for 72 hours). Followed by oral therapy according to improvement. H_2 receptor antagonists are of no value.

7. Endoscopy of upper GIT should be performed after resuscitation. When applicable, patient may be treated with heater probe, injection of dilute adrenaline or by metallic clips to stop bleeding.
8. Pulse, BP and urine output should be monitored hourly.
9. Surgical management—urgent surgery is indicated when:
   - Endoscopic management fails to stop active bleeding
   - Rebleeding occurs on one occasion in an elderly or frail patient, or twice in younger fit patient.

Remember the following:

- If the patient is suffering from chronic peptic ulcer, eradication therapy for *H. pylori* should be started as early as possible.
- PPI should be continued for 4 weeks to ensure healing.

Q. What are the **predictors for adverse prognosis** in upper GIT bleeding?

A. The following factors affect the risk of rebleeding and death:

- Age more than 60 years
- Presence of other diseases like cardiac failure, IHD, renal disease like CRF, and malignancy
- Clinical signs of chronic liver disease
- Presentation of patient with shock (pallor, cold extremities, systolic BP < 100 mm Hg, pulse > 100/min)
- Ulcer with active bleeding or stigmata of recent bleeding at endoscopy (i.e. a spurting artery, active oozing, fresh or organized blood clot or black spots).

Note Remember the following:

- Scoring systems may be used to assess the risk of rebleeding or death. Rockall score, which is based on clinical and endoscopic findings (as above). Another system called Blatchfort score uses the level of plasma urea, hemoglobin and clinical markers but not endoscopic finding.
- Rebleeding (fresh hematemesis or melena associated with shock or a fall of Hb > 2 g/dL over 24 hours) is associated with a 10 fold rise in mortality.
- Varices and cancer have the worst prognosis.

Q. What are the **complications of surgical management** of PUD (gastric resection or vagotomy)?

A. As follows:

1. Recurrent ulcer (check for *H. pylori* and also rule out Zollinger-Ellison syndrome).
2. Dumping syndrome: This occurs following gastrectomy or gastrojejunostomy.
   - Early dumping syndrome: It occurs 15 to 30 minutes after a meal, especially after taking sweet food. Rapid gastric emptying of food into the jejunum causes rapid fluid shift from plasma into the lumen, resulting in reduction of blood volume. The patient complains of nausea, abdominal distension associated with flushing, palpitation, faintness, sweating, tachycardia and hypotension. This is usually mild and patients adapt themselves. Reassurance is sufficient.
   - The late dumping syndrome: It occurs 2 to 3 hours after meal which is due to hypoglycemia. The patient complains of sweating, light-headedness, palpitations and occasional syncope. In such case, the patient should avoid taking large meals with high carbohydrate content. Instead, they should take small amounts of food at frequent intervals. Anticholinergic agents or subcutaneous octreotide may be given.
3. Bile reflux gastritis.

4. Diarrhea, mostly after vagotomy.
5. Nutritional:
   - Iron deficiency anemia, due to poor absorption
   - Vitamin B_{12} deficiency anemia, due to lack of intrinsic factor
   - Folic acid deficiency, due to poor intake and absorption of food
   - Osteomalacia and osteoporosis, due to vitamin D and calcium deficiency respectively
   - Weight loss, due to less intake of food or malabsorption.
6. Carcinoma stomach after partial gastrectomy.

Q. What is **non-ulcer dyspepsia?**

A. It is defined as "chronic dyspepsia characterized by pain or upper abdominal discomfort without any organic cause". The cause is unknown, but probably due to spectrum of mucosal motility and psychiatric disorder. The patient is usually young (< 40 years), women are twice more affected.

Symptoms are pain or upper abdominal discomfort, early satiety, fullness, bloating and nausea after a meal. Symptoms are more in the morning. There is no weight loss. Features like IBS may be present. Sometimes, these two conditions may exist together. The patient may look anxious. Symptoms may be disproportionate to clinical well being. Abdomen may be inappropriately tender on palpation.

Diagnosis is often apparent from history. No investigation is needed if the patient is less than 50 years. For older patients or those with alarming symptoms, endoscopy should be done to exclude other disease. In young female, pregnancy should be excluded. Other investigations include USG of whole abdomen (to exclude hepatobiliary or pancreatic disease), liver function test, CBC, OBT, colonoscopy, CT abdomen when appropriate.

Treatment:

- In majority of cases, explanation, reassurance and lifestyle change
- Restriction of fat, coffee, alcohol
- Cigarette smoking must be stopped
- Drug treatment—antacids, prokinetic drugs (metoclopramide, domperidone) if nausea, vomiting or bloating is prominent, H_2 blockers if night pain or heartburn is prominent. PPI may be given as well. Low dose amitriptyline may be helpful.
- *H. pylori* eradication regimen may be given. It is helpful in some case, but the role is controversial.
- Psychotherapy may be given.

Q. What are the **functional disorders** of GIT?

A. It may be in the esophagus, small gut or large gut.

1. Functional esophageal disorder:
   - Heartburn
   - Chest pain
   - Dysphagia
   - Globus.
2. Functional gastroduodenal disorder:
   - Non-ulcer dyspepsia
   - Nausea and vomiting disorder
   - Rumination syndrome (persistent effortless regurgitation of recently swallowed food into the mouth with subsequent remastication and reswallowing)
   - Belching disorder.

3. Functional bowel disorder:
   - Irritable bowel syndrome
   - Functional bloating
   - Functional constipation
   - Functional diarrhea
   - Unspecified functional bowel disorder.
4. Functional abdominal pain syndrome.
5. Functional gall bladder and sphincter of Oddi disorder.

CHRONIC DUODENAL ULCER WITH PYLORIC STENOSIS

CHIEF COMPLAINTS

- Nausea, abdominal discomfort and vomiting for … months
- Weight loss for … months
- Constipation for … months.

HISTORY

History of present illness: According to the patient's statement, he has been suffering form chronic duodenal ulcer for … years. But for the last … months, his abdominal pain has subsided and he has been suffering from nausea, abdominal discomfort after taking food and repeated vomiting. Vomiting is painless, projectile, large in volume, contains previous day's food, but there is no blood or bile. The patient admits occasional self-induced vomiting, which relieves his abdominal discomfort. He also complains of weakness, constipation and substantial loss of weight for the last … months. There is no history of hematemesis or melena.

History of past illness: He was suffering from peptic ulcer disease for 15 years.

Family history: There is no such illness in his family.

Personal history: He is a farmer, used to take food irregularly. He smokes 20 sticks a day for the last 10 years but non alcoholic.

Socioeconomic history: He is from lower socioeconomic condition and lives in a remote rural area.

Drug history: He used to take antacid, omeprazole and ranitidine frequently for PUD.

GENERAL EXAMINATION

- Ill looking, emaciated and dehydrated
- Moderately anemic
- No jaundice, cynosis, clubbing, koilonychia, leukonychia or edema
- Lymphadenopathy or thyromegaly absent
- Pulse: 100/min
- BP: 100/70 mm Hg
- Temperature: 98ºF
- Respiratory rate: 16/min.

SYSTEMIC EXAMINATION

Gastrointestinal System

Lips, gums, teeth, tongue and oral cavity—mention according to the finding.

Abdomen:

Inspection:

- Abdomen is distended, mostly in upper part
- Visible peristalsis—present, from left to right.

Palpation:
- No rigidity or tenderness
- Liver—not palpable
- Spleen—not palpable
- Kidneys—not ballotable
- Succussion splash—present

Percussion: No abnormality detected (may be tympanitic).
Auscultation: Bowel sound is increased.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mr … 48-year-old, farmer, normotensive, nondiabetic, smoker, hailing from …, has been suffering form chronic duodenal ulcer for … years. But for the last … months, his abdominal pain has subsided and he has been suffering from nausea, abdominal discomfort after taking food and repeated vomiting. Vomiting is painless, projectile, large in volume, contains previous day's food, but there is no blood or bile. The patient admits occasional self-induced vomiting, which relieves his abdominal discomfort. He also complains of weakness constipation and substantial loss of weight for the last … months. There is no history of hematemesis or melena. He was suffering from peptic ulcer disease for 15 years. There is no such illness in his family. He used to take food irregularly. He smokes 20 sticks a day for the last 10 years but non alcoholic. He is from lower socioeconomic condition and lives in a remote rural area. He used to take antacid, omeprazole and ranitidine frequently for PUD.

On examination—general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is chronic duodenal ulcer with gastric outlet obstruction (pyloric stenosis).

Q. What are the **causes** of GOO?

A. As follows:
- Chronic duodenal ulcer
- Carcinoma of pylorus
- Adult hypertrophic pyloric stenosis (rare)
- Others—Crohn's disease, compression by pancreatic carcinoma.

Q. What are your **differential diagnoses**?

A. As follows:
- Gastric outlet obstruction due to carcinoma of stomach (or rarely, gastric lymphoma).
- Gastric outlet obstruction due to adult hypertrophic pyloric stenosis.

Q. **Why not** this is a case of carcinoma of the stomach?

A. Because there is long history of duodenal ulcer, and now at present there is loss of pain and also periodicity. Also in carcinoma of stomach, there is marked loss of weight and survival is also short.

Q. How to **confirm** your diagnosis?

A. Endoscopy of the upper GIT, barium meal X-ray of the stomach and duodenum may be done.

Q. What **investigations** do you suggest?

A. As follows:
- CBC with ESR

- Serum electrolytes
- Blood urea, serum creatinine
- Endoscopy of the upper GIT with biopsy (if needed)
- Barium meal X-ray of the stomach and duodenum
- USG of the whole abdomen to exclude other causes.

RELATED QUESTIONS AND ANSWERS

Q. What are the **features of gastric outlet obstruction** (or pyloric stenosis)?

A. As follows:

- History of peptic ulcer
- Loss of pain and periodicity
- Anorexia, nausea and vomiting (profuse and projectile, occasionally self induced). Vomitus contains previous day's food. Patient feels better after vomiting
- Food habit: The patient eats breakfast, a little lunch and little or nothing at dinner
- Abdominal distension, weight loss and constipation
- Succussion splash present 4 hours or more after the last meal or drink
- Visible gastric peristalsis.

Q. What are the **electrolyte abnormalities** in pyloric stenosis?

A. As follows:

- Sodium and chloride—low
- Potassium—low
- Bicarbonate—high (metabolic alkalosis)
- Urea—high.

Q. Why is **potassium low**?

A. Due to:

- Repeated vomiting (less potassium is lost).
- Metabolic alkalosis due to vomiting, which causes potassium to enter into the cells.
- Secondary aldosteronism which causes renal K^+ excretion.
- Hyponatremia and metabolic alkalosis results in renal reabsorption of sodium and hydrogen in exchange of excretion of potassium (loss of potassium by kidney is much more than by vomiting).

Note

When serum potassium level is very low, the kidney starts to excrete hydrogen in exchange of sodium leading to aciduria despite metabolic alkalosis. This is called paradoxical aciduria.

Q. How will you **manage** the case?

A. As follows:

- Resuscitation of the patient. Correction of dehydration and electrolyte imbalance (normal saline 3 to 4 L and potassium).
- Nasogastric aspiration may be given.
- Surgery—partial gastrectomy or gastrojejunostomy with vagotomy followed by PPI to prevent stomal ulceration.
- Endoscopic dilatation may be done.

CARCINOMA OF THE STOMACH

CHIEF COMPLAINTS

- Upper abdominal pain, loss of appetite, discomfort, nausea and vomiting for … months
- Weakness and weight loss for … months.

HISTORY

History of present illness: According to the statement of the patient, he was alright … months back. Since then, he has been suffering from upper abdominal pain, loss of appetite, abdominal discomfort, nausea and vomiting. The pain is dull aching in nature, constant, aggravated by taking food and does not radiate to any site. It occasionally reduces after taking antacid. He also complains of occasional vomiting, which occurs after taking food, the vomitus contains the food materials but no blood or bile. There is no history of induced or projectile vomiting. The patient also complains of weakness, marked loss of appetite and significant weight loss for the last … months. There is no history of melena, cough or evening rise of temperature. His bowel and bladder habits are normal.

History of past illness

Family history

Personal history

Socioeconomic history

Drug history: Mention according to the patient's statement.

GENERAL EXAMINATION

- Ill looking and grossly emaciated
- Moderately anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or no thyromegaly
- Pulse: 120/min
- BP: 90/70 mm Hg
- Temprature: 97ºF
- Respiration: 20/min.

SYSTEMIC EXAMINATION

Gastrointestinal System

Lips, gums, teeth, tongue and oral cavity—mention according to the finding.

Abdomen:

Inspection: No abnormality detected (may be visible mass in epigastrium or distension of upper abdomen).

Palpation:

- There is an ill-defined mass in the epigastric region, 2 × 3 cm, margin irregular, nontender, firm in consistency, surface slightly irregular, mobile from side to side.

- Liver—not palpable.
- Spleen—not palpable.
- Kidneys—not ballotable.
- Succussion splash—absent.

Percussion: No abnormality detected.
Auscultation: No abnormality detected.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mr … 64-year-old, businessman, non-hypertensive, nondiabetic, smoker, hailing from …, presented with upper abdominal pain, loss of appetite, abdominal discomfort, nausea and vomiting. The pain is dull aching in nature, constant, aggravated by taking food and does not radiate to any site. It occasionally reduces after taking antacid. He also complains of occasional vomiting, which occurs after taking food, the vomitus contains the food materials but no blood or bile. There is no history of induced or projectile vomiting. The patient also complains of weakness, marked loss of appetite and significant weight loss for the last … months. There is no history of melena, cough or evening rise of temperature. His bowel and bladder habits are normal.

There is no history of such illness in his family. He used to smoke about 20 sticks of cigarettes for the last 40 years but not alcohol.

For his symptoms, local doctor prescribed tablet ranitidine and antacid, but his symptoms did not improve.

On examination—general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is gastric outlet obstruction due to carcinoma of the stomach.

Q. What are your **differential diagnoses?**

A. As follows:

- Gastric outlet obstruction due to chronic duodenal ulcer with pyloric stenosis.
- Gastric lymphoma.

Q. **Why not** this is chronic duodenal ulcer?

A. There is no history of long standing duodenal ulcer, and also there is marked anorexia, rapid loss of weight and also there is a mass in the epigastric region.

Q. **What else** have you seen in association of the epigastric mass?

A. Enlargement of left supraclavicular lymph node (Virchow's gland), called Troisier's sign.

Q. How to **confirm** your diagnosis?

A. Endoscopy of upper GIT with biopsy.

Q. What other **investigations** do you suggest in this case?

A. As follows:

- Hb%, TC, DC, ESR.
- USG of whole abdomen (to see the origin of the mass like liver, stomach, transverse colon, pancreas or secondary in the liver from carcinoma of stomach).
- Barium meal (filling defect, irregular ulcer, in infiltrating type—stomach looks like tube).
- Stool for occult blood test.
- To see recurrence—CEA may be done.

RELATED QUESTIONS AND ANSWERS

Q. What are the **presentations** of carcinoma of stomach?

A. As follows:

- Any patient above 40 years of age presenting with "**3 A**" (Anemia, Anorexia, Asthenia).
- Vomiting (if tumor in the pyloric end).
- Pain in the epigastrium.
- Dysphagia (if tumor in the cardiac end).
- Hematemesis and melena.
- Mass in the epigastrium.
- Only unexplained features of anemia.
- Features of metastasis:
  - Hepatomegaly
  - Virchow's gland
  - Hard nodule around umbilicus (Sister Mary Joseph's nodule)
  - Ovarian involvement (Krukenberg's tumor)
  - Pre-rectal pouch—a shelf-like mass (Blumer's shelf).
- Paraneoplastic syndrome (acanthosis nigricans, dermatomyositis, thrombophlebitis migrans).

Q. What are the **types** of carcinoma of stomach?

A. As follows:

1. Macroscopic—4 types:
   - Polypoid
   - Ulcerative
   - Fungating or cauliflower
   - Diffuse infiltrative—linitus plastica (rare).
2. Microscopic:
   - Adenocarcinoma (95%): 2 types :
     - Intestinal (better prognosis)
     - Diffuse (bad prognosis).
   - Others:
     - Squamous cell carcinoma
     - Non-Hodgkin's lymphoma
     - Leiomyosarcoma.

Q. What are the **causes** or predisposing factors for carcinoma of stomach?

A. Causes are unknown. Predisposing factors are:

1. Diet:
   - Preservatives in diet such as nitrates. It is converted to nitrosamines, which is carcinogenic. Nitrate is converted by the nitrite reducing bacteria which colonize in achlorhydric stomach.
   - Excess spicy, salted and pickled food.
   - Diet lacking fresh fruits and vegetables as well as vitamin C and A may be contributing factors.
2. Smoking.
3. Alcohol.
4. Gastric surgery (partial gastrectomy, gastrojejunostomy). Carcinoma is due to intestinal metaplasia and chronic gastritis, probably due to untreated *H. pylori* infection also.
5. Infection with *Helicobacter pylori* that cause chronic gastritis, that eventually leads to atrophic gastritis and intestinal metaplasia, which is premalignant. This organism may be responsible in

60 to 70% case, mostly associated with achlorhydria. Chronic inflammation with generation of reactive oxygen species and depletion of antioxidant ascorbic acid are also important.

6. Others—pernicious anemia, familial adenomatous polyposis, Menetriere's disease, blood group-A, first degree relative.

Q. What are the **sites** of carcinoma stomach?

A. As follows:

- Antrum—50%
- Body of the stomach (greater curvature)—20 to 30%
- Cardiac end of stomach—20%.

In the western population, proximal gastric tumors are becoming more common than those arising in the body or distal stomach.

Q. What is the **benign tumor** of stomach?

A. Leiomyoma.

Q. How to **treat** a case of carcinoma stomach?

A. As follows:

1. Surgery is the only curative treatment. 5 year survival is 90% if surgery is done in early gastric cancer, but only 10% if done in advanced cases.
2. Perioperative chemotherapy—ECF (epirubicin, cisplatin and fluorouracil) has improved 5 year survival in operable gastric and lower esophageal adenocarcinoma.
3. Chemotherapy- not much helpful. **FAM** (combination of 5-Fluorouracil + adriamycin + mitomycin C) may be tried.
4. Palliative:
   - Radiotherapy—very little role.
   - Endoscopic laser ablation of tumor tissue may be done if surgery is not possible.
   - Endoscopic dilatation or insertion of expandable metallic stents may be used for relief of dysphagia or vomiting.

Q. What is **early gastric cancer**?

A. When carcinoma is confined to mucosa or submucosa regardless of lymph node involvement, it is called early gastric cancer. It is associated with 5 years survival of about 90%. Many may survive 5 years even without treatment. It may be cured by endoscopic mucosal resection or endoscopic submucosal dissection.

Q. What is **linitus plastica**?

A. It means diffuse submucosal infiltration of schirrous carcinoma. Stomach becomes a rigid tube. Other causes of linitus plastica include lymphoma, sarcoidosis, secondary syphilis and gastric lymphoma.

Gastric Lymphoma

It is the second most common neoplasm of stomach. Among the GIT lymphoma, 60% occur in the stomach. 95% is low grade non-Hodgkin's B-cell type. Gastric lymphoma may be:

- Primary—arise from mucosa associated lymphoid tissue (MALT).
- Secondary to lymph node involvement in other parts of the body.

Primary gastric lymphoma may be due to *Helicobacter pylori* infection. 85% are low grade and 40% are high grade when associated with *H. pylori* infection. Chronic antigenic stimulation result in monoclonal lymphoproliferation that may cause low grade MALT lymphoma.

Symptoms: Similar to that of gastric cancer. Patients with primary gastric lymphoma have stomach pain, ulcers or other localized symptoms but systemic complaints such as fatigue or fever are rare.

Diagnosis: By endoscopy and biopsy. At endoscopy, the tumour usually appears as a polypoid or ulcerating mass.

Treatment:

- **Primary type:** Treatment with anti-*Helicobacter* therapy may regress the tumor. If no response, other therapy for lymphoma should be given (radiotherapy or chemotherapy).
- **Secondary type:** Usual therapy for lymphoma (chemotherapy, radiotherapy).

Prognosis: Varies according to the type. Features predicting a favorable prognosis are stage I or II disease, small resectable tumor or tumor with low grade histology, and age below 60 years.

CARCINOMA HEAD OF THE PANCREAS

CHIEF COMPLAINTS

- Pain in epigastric region for … months
- Loss of appetite and weight loss for … months
- Yellow discoloration of the skin, eyes and urine for the last … days
- Severe generalized itching for … days.

HISTORY

History of present illness: According to the statement of the patient, she was alright … months back. Since then, she has been suffering from pain in epigastric region, which is deep seated, dull aching in nature, radiates to the back and is aggravated by taking food. Pain is more marked while lying flat, and slightly reduced on bending forward. She also complains of gradual loss of appetite and marked weight loss for … months. The patient also noticed yellow discoloration of skin, eyes and urine for last … days, which is progressively increasing. Jaundice is not preceded by any prodromal symptoms like anorexia, nausea, vomiting, etc. For the last … days, she is also experiencing severe generalized itching and occasional diarrhea. The stool was initially yellowish, but for the last … days, it is clay or muddy, or whitish colored and voluminous. There is no history of vomiting, hematemesis, melena, fever or cough.

History of past illness

Family history

Personal history

Socioeconomic history

Drug history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient is extremely ill looking and grossly emaciated, also pigmented
- Severely anemic and also severely icteric
- Scratch mark present on different parts of the body
- No cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or no thyromegaly
- Pulse: 108/min
- BP: 90/65 mm Hg
- Temperature: 97ºF
- Respiration: 20/min.

SYSTEMIC EXAMINATION

Gastrointestinal System

Lips, gums, teeth, tongue and oral cavity—mention according to the finding.

Abdomen:

Inspection: No abnormality detected.
Palpation:
- There is an ill-defined mass in the epigastric region, 2 × 3 cm in size, margin is irregular, nontender, hard in consistency, surface is irregular, not freely mobile.
- Liver—not palpable.
- Spleen—not palpable.
- Kidneys—not ballotable.
- Succusion splash—absent.

Percussion: No abnormality detected.
Auscultation: No abnormality detected.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mrs … 65-year-old, housewife, normotensive, nondiabetic, non-smoker, hailing from …, presented with pain in epigastric region for … months, which is deep seated, dull aching in nature, radiates to the back and is aggravated by taking food. Pain is more marked while lying flat, and slightly reduced on bending forward. She also complains of gradual loss of appetite and marked weight loss for … months. The patient also noticed yellow discoloration of skin, eyes and urine for last … days, which is progressively increasing. Jaundice is not preceded by any prodromal symptoms like anorexia, nausea, vomiting, etc. For the last … days, she is also experiencing severe generalized itching and occasional diarrhea. The stool was initially yellowish, but for the last … days, it is clay or muddy, or whitish coloured and voluminous. There is no history of vomiting, hematemesis, melena, fever or cough. She used to take some drugs prescribed by local physicians, the name of which she cannot mention. There is no family history of such illness.

On examination—general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is obstructive jaundice probably due to carcinoma head of the pancreas.

Q. What are your **differential diagnoses?**

A. Obstructive jaundice due to:
- Carcinoma of the ampulla of Vater
- Periampullary carcinoma
- Cholangiocarcinoma
- Stricture of common bile duct or sclerosing cholangitis.

Q. Suggest **one single investigation** in this case.

A. Ultrasonogram of upper abdomen.

Q. What **other investigations** do you suggest?

A. As follows:
- Liver function test (bilirubin, SGPT, alkaline phosphatase, prothrombin time, etc. Alkaline phosphatase is usually very high)
- Barium meal X-ray with C-loop (it will show widening of the C-loop)
- CT scan of abdomen
- MRI scan and endoscopic ultrasound are helpful in some cases

- CT or ultrasound guided FNAC—may be done but not in potentially operable case. It may spread the malignancy to the peritoneum
- Blood glucose
- Tumor markers especially CA 19-9 is highly sensitive (80%) but false positive result may be found
- ERCP (to see obstruction, irregularity or distortion of pancreatic duct. Also, helpful to insert stent in obstructive jaundice)
- MRCP may be done
- Sometimes, laparoscopy and laparoscopic USG (in very small lesion).

RELATED QUESTIONS AND ANSWERS

Q. What are the causes of **epigastric mass**?

A. As follows:

- Carcinoma of stomach
- Carcinoma of the head of the pancreas
- Hepatic mass (hepatoma, secondary, liver abscess, hydatid cyst)
- Carcinoma of transverse colon
- Gall bladder mass—such as carcinoma
- Mucocele or empyema of the gallbladder
- Pseudocyst of pancreas
- Epigastric hernia.

Q. What are the **causes** of carcinoma head of pancreas?

A. Actual causes are unknown. Some factors are responsible:

- Age, above 70 years
- Male, predominant (twice more than female)
- Chronic pancreatitis
- Alcohol
- Smoking
- Environmental factors, such as petroleum product and naphthylamine
- Genetic in 5 to 10% cases. There may be hereditary pancreatitis, multiple endocrine neoplasia (MEN) and hereditary non-polyposis colon cancer (HNPCC).

Q. What are the **types** of carcinoma of pancreas and what are the **sites?**

A. Usually adenocarcinoma (90%), which arises from the epithelium of pancreatic duct. Sites are as follows:

- 60% in head
- 25% in body
- 15% in tail.

Q. What are the **presentation**s of carcinoma of the pancreas?

A. As follows:

- Painless obstructive jaundice, with palpable gallbladder—in case of carcinoma of head of pancreas.
- Carcinoma involving the body and tail – usually presents with pain in the epigastrium, deep seated, dull aching, radiates to the back, more on lying flat, feels better with bending forward (pain is due to involvement of celiac plexus)
- Loss of weight, anorexia, nausea
- Mass in upper abdomen (in 20% cases)

- Others—diabetes mellitus, acute pancreatitis
- Rare features are—thrombophlebitis migrans (arm vein is more involved than leg vein), venous thrombosis, portal hypertension and marantic endocarditis.

Note

Courvoisier's law: In a jaundiced patient with palpable gallbladder, the cause is unlikely to be gallstones, rather it is due to carcinoma head of pancreas and extrinsic pressure in bile duct. (Reverse of the law—Obstructive jaundice without palpable gallbladder is unlikely to be due to carcinoma head of pancreas and extrinsic pressure in common bile duct.)

Q. How to **treat** carcinoma head of pancreas?

A. As follows:

1. In early stage, surgical resection (Whipple's operation is performed. In this operation, pancreas, duodenum, draining lymph node and part of mesentery are removed). About 5-year survival is 20% after surgery. Survival is improved with adjuvant chemotherapy (5-FU).
2. Other treatment (usually palliative):
   - Endoscopic insertion of stent to relieve intractable itching.
   - For pain—analgesic, injection of alcohol in celiac plexus (USG guided or endoscopic USG guided).
   - Chemotherapy—5FU, adriamycin and cisplatin may be tried. Combination of 5FU plus gemcitabine may help to improve the survival in advanced disease.
   - Radiotherapy is not much helpful.

Q. What is the **prognosis?**

A. Prognosis is bad, mean survival is < 6 months. Usual 5 year survival is 2 to 5%. Following Whipples' operation, 5 year survival is 5 to 14% (may be up to 20%). If adjuvant chemotherapy is given with 5-fluorouracil, then 5 year survival becomes 21 to 29%. Prognosis is better if tumor size < 3 cm, no lymph node involvement, negative resection of margin at surgery, ampulary or islet cell tumors.

INFLAMMATORY BOWEL DISEASE

CHIEF COMPLAINTS

- Frequent loose motion with mucus for … months
- Abdominal pain for … months
- Recurrent mouth ulcer for … months
- Weight loss and loss of appetite … months.

HISTORY

History of present illness: According to the statement of the patient, she was alright … months back. Since then, she has been suffering from occasional loose motion, 4 to 6 times daily, often mixed with mucus, but not blood. It is not related to any food or drug. She also complains of sense of incomplete evacuation of bowel and occasional abdominal pain. The pain is mostly around the umbilicus, colicky in nature, mild to moderate in intensity, radiates to the back, persists for minutes to few hours, not related to food intake and sometimes relieved by defecation. For the last ... months, she noticed recurrent painful mouth ulcer. She also complains of loss of appetite and significant weight loss during this period. There is no history of any perianal pain, joint pain, eye-problem, fever, cough, any skin rash, ulceration or nodules or contact with tuberculosis patient.

History of past illness: She suffered from similar illness several times over the last 2 years and was hospitalized once.

Family history

Personal history

Socioeconomic history

Drug history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient is emaciated and ill looking
- Moderately anemic
- There are generalized clubbing involving fingers and toes
- No jaundice, cyanosis, koilonychia, leukonychia and edema
- No lymphadenopathy or no thyromegaly
- Pulse: 88/min
- BP: 120/75 mm Hg
- Temperature: 98ºF
- Respiratory rate: 18/min.

SYSTEMIC EXAMINATION

Gastrointestinal System

Lips, gums, teeth—normal. There is one ulcer in the inner part of the right side of the cheek (aphthous ulcer). Lips (may be) swollen.
Tongue—pale.

Abdomen

Inspection: No abnormality detected (there may be visible peristalsis, that moves from above downwards, multiple fistula, scar mark, ileostomy bag, etc.)

Palpation:

- Liver—not palpable.
- Spleen—not palpable.
- Kidneys—not ballotable.
- Succusion splash—absent.

Percussion: No abnormality detected.

Auscultation: No abnormality detected.

Per-rectal examination:

- Inspection—a fistula is noted on the 3o' clock position of the anus.
- Digital Rectal Examination—no abnormality detected.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mrs …, 46-years-old, housewife, normotensive, nondiabetic, nonsmoker, hailing from …, presented with occasional loose motion, 4 to 6 times daily for … months. It is often mixed with mucus, but not blood. It is not related to any food or drug. She also complains of sense of incomplete evacuation of bowel and occasional abdominal pain. The pain is mostly around the umbilicus, colicky in nature, mild to moderate in intensity, radiates to the back, persists for minutes to few hours, not related to food intake and sometimes relieved by defecation. For the last ... months, she noticed recurrent painful mouth ulcer. She also complains of loss of appetite and significant weight loss during this period. There is no history of any perianal pain, joint pain, eye-problem, fever, cough, any skin rash, ulceration or nodules or contact with tuberculosis patient. She suffered from similar illness several times over the last 2 years and was hospitalized once. She used to take pain killers, ranitidine and omeprazole. One of his maternal uncle suffered from similar illness.

On examination—general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is IBD, more likely to be Crohn's disease.

Q. What are your **differential diagnoses?**

A. As follows:

- Ileocecal tuberculosis
- Lymphoma
- Ulcerative colitis
- IBS
- Chronic pancreatitis.

Q. What are the **sites** of Crohn's disease?

A. Any part of gastrointestinal tract, from mouth to anus, may be involved, but commonly terminal ileum is involved (hence, it was previously called regional ileitis). In order of frequency, ileum and right side of colon, colon alone, terminal ileum alone, ileum and jejunum. Lesion is transmural (all layers are involved). The disease can involve a small area of the gut, or multiple areas with relatively normal bowel in between them, called "skip lesion".

Q. What **investigations** should be done in Crohn's disease?

A. As follows:

- CBC (anemia is usually normocytic, may be megaloblastic due to vitamin B_{12} deficiency)
- ESR and CRP (both high)
- Total protein and A/G ratio (low albumin)
- Liver function tests (may be abnormal)
- Blood for C/S (if septicemia is suspected)
- Stool for R/E and C/S (to exclude infective cause like *Salmonella, Shigella, Campylobacter, E. coli, Clostridium difficile*)
- USG of whole abdomen
- Barium follow through or small bowel enema (detects ileal disease, there may be narrowing of the affected segment, called string sign, which is pathognomonic of Crohn's disease)
- Barium enema
- Colonoscopy (in colonic Crohn's disease) with ileoscopy and biopsy
- Enteroscopy
- Capsule endoscopy (in assessing small bowel disease)
- CT scan or MRI of abdomen.

RELATED QUESTIONS AND ANSWERS

Q. What is **Crohn's disease**? What are the **presentations**?

A. Crohn's disease is a chronic inflammatory disease of unknown etiology involving any part of gastrointestinal tract, commonly the terminal ileum. It is slightly common in female, M:F = 1:1.2, more in young (mean age is 26 years). Common presentations are as follows:

- Frequent diarrhea
- Abdominal pain (colicky)
- Weight loss
- Failure to thrive in children
- Other systemic features are malaise, lethargy, low grade fever, anorexia, nausea, vomiting
- Extra-intestinal manifestations (see below)
- Sometimes, it may present with acute emergency like acute appendicitis. If laparotomy is done, terminal ileum looks edematous and red
- Sometimes, the patient may present with recurrent aphthous ulceration of mouth, mass in right iliac fossa (due to inflamed loops of bowel matted together or abscess), anal fissures or perianal abscess.

Q. What are the **extra-intestinal manifestations** of Crohn's disease?

A. As follows:

- Eyes—conjunctivitis, episcleritis, uveitis or iritis.
- Mouth—aphthous ulcer and thickened lip.
- Skin—erythema nodosum, pyoderma gangrenosum or fistula in abdominal wall.
- Bones and joints—acute peripheral arthritis (occurs in 15 to 20%, related to active disease, treatment of Crohn's disease improves the condition. In severe case, even colectomy improves arthritis). Sometimes, ankylosing spondylitis or sacroiliitis and clubbing may also occur.
- Perianal region—perianal fistula, skin tag and abscess.
- Liver or hepatobiliary—fatty liver, pericholangitis, sclerosing cholangitis (common in ulcerative colitis), autoimmune hepatitis, cirrhosis of liver, granuloma, liver abscess or portal pyemia, gall stone and cholangiocarcinoma.

- Kidney—nephrolithiasis (oxalate stone), hydronephrosis and pyelonephritis.
- Others—amyloidosis and venous thrombosis.

Q. What are the **complications** of Crohn's disease?

A. As follows:

- Intestinal obstruction
- Enteric fistula to bladder or vagina
- Abscess formation
- Perianal disease (fissure, skin tag, fistula, perianal abscess, hemorrhoid)
- Carcinoma (rare, may occur if Crohn's disease involves the colon)
- Toxic dilatation of the colon (more common in ulcerative colitis)
- Malabsorption syndrome.

Q. What are the **causes** of Crohn's disease?

A. Actual causes unknown. Probable factors are:

- Genetic and familial
- Diet—high sugar and fat, but low residue diet
- Smoking
- Probable association with mycobacteria and measles virus (not proved)
- Abnormal immunological response.

Note Remember the following points:

- Appendicectomy is protective of ulcerative colitis, but may increase the risk of Crohn's disease or may result in more aggressive disease.
- Oral contraceptive pill increases the risk of Crohn's disease.

Q. What is the **relation of smoking** in IBD?

A. In smokers, the incidence of Crohn's disease is high. But there is increased risk of ulcerative colitis in nonsmoker or ex-smokers.

Q. How to assess the **activity** of Crohn's disease?

A. Signs of activity are:

1. Clinical:
   - Eye signs—episcleritis, conjunctivitis and iritis
   - Mouth—aphthous ulcer
   - Skin—erythema nodosum and pyoderma gangrenosum
   - Arthralgia of large joints
   - Fatty liver or liver abscess or portal pyemia
   - Mesenteric or portal vein thrombosis
   - Venous thrombosis (in other veins).
2. Morphology—by radiological or endoscopy
3. Laboratory:
   - Low albumin (due to protein losing enteropathy)
   - High ESR
   - High C-reactive protein (CRP).
4. Scanning with white cell labelled with ^{111}Indium or ^{99m}Tc to locate active site.

Q. What are the types of **arthritis** in Crohn's disease?

A. Peripheral arthropathy is common, which may be of two types:

- Type 1, Pauciarticular—usually acute, self limiting, < 10 weeks duration, occur with IBD relapses, usually associated with other extra-intestinal features of IBD. Indicates active disease.
- Type 2, Polyarticular—last longer (months to years), not related to IBD activity, usually associated with uveitis.

Other types are—ankylosing spondylitis, arthralgia, inflammatory back pain. These are not related to IBD disease activity.

Q. How to **treat** Crohn's disease?

A. Induction of remission in active disease and maintenance of remission.

1. Induction of remission:
   a. General measures:
      - Diet, with high protein, low fat and milk free. If needed, enteral or parenteral feeding.
      - For anemia—supplement of iron, B12, folic acid and zinc. Erythropoietin may be given.
      - Symptomatic treatment for diarrhea (loperamide, codeine phosphate or cophenotrope). In long standing diarrhea, cholestyramine may be helpful.

   b. Drugs:
      - Prednisolone—40 to 60 mg/day. Budenoside may be used in moderately active disease.
      - Combination of prednisolone and azathioprine or 6 mercaptopurine (6MP) may be used.
      - For perianal disease, metronidazole (400 mg bd for 14 days) plus ciprofloxacin may be given. 6MP or azathioprine may be used in chronic case. Infliximab and adalimumab are effective in healing fistula and perianal disease.
      - In active and moderate to severe total Crohn's colitis or ileocolitis, treatment is like active ulcerative colitis, as follows:
        – Oral and per-rectal aminosalicylate plus per-rectal steroid should be given.
        – Oral prednisolone is indicated for more active disease or when aminosalicylate is ineffective.
        – In more severe colitis or in patient who fails to maximum oral therapy, patient should be hospitalized and treated as follows:
          - IV fluid and nutritional support.
          - IV methylprednisolone or hydrocortisone 100 mg 6 hourly.
          - Topical and oral aminosalicylates are also used.
          - If the patient does not respond to steroid therapy, then IV cyclosporine or infliximab may be given. Otherwise urgent surgery should be done.

2. Maintenance of remission:
   - Smoking must be stopped.
   - Aminosalicylate may be given, but has minimal efficacy.
   - Thiopurines (azathioprine or 6-MP) is given in patient who relapses more than once a year.
   - If it fails, weekly MTX should be given.
   - In aggressive disease, combination of immuosuppressive and anti TNF therapy should be given.

3. In resistant cases (to steroid or immunosuppressive) or failure of above therapy, the following treatment may be given:
   - Methotrexate
   - IV cyclosporine
   - Anti-TNF antibody, e.g. infliximab may be given in infusion 4 to 8 weekly, in three occasions. Aslo, adalimumab may be used. Relapse usually occurs after 12 weeks. So, MTX or azathioprine or 6-MP should be added to maintain remission (etanercept is ineffective).

Infliximab helps in healing fistula and perianal disease. These agents are contraindicated in presence of infection including tuberculosis. Allergic reaction may occur.

4. Surgical management: Surgery should be avoided if possible and only minimum resection should be done, as the disease is multicentric and recurrence is almost inevitable. Indications of surgery are:
   - Failure of medical therapy, intractable disease or fulminant disease.
   - Complications like toxic megacolon, obstruction, perforation, massive hemorrhage, refractory fistula and abscess, etc., which are not responding to medical treatment.
   - Extra-intestinal complications like severe arthritis or pyoderma gangrenosum, not responding to medical treatment.
   - Failure to grow in children despite medical treatment.
   - Suspicion of malignancy or severe dysplasia.

Recurrence is common after surgery. If second surgery is needed, azathioprine or 6MP should be added to prevent recurrence. There is no strong benefit, if it is given after first surgery.

Note Remember the following:

Prednisolone has no role to prevent recurrence.

Q. What are the **differential diagnoses** of Crohn's disease?

A. As follows:

1. Infectious conditions:
   - Bacterial—salmonella, shigella, ETEC, campylobacter, pseudomembranous colitis, Chlamydia proctitis, gonococcal proctitis.
   - Viral—herpes simplex proctitis, HIV, CMV.
   - Parasitic—amebiasis, strongyloidiasis, isospora.
2. Non infectious:
   - Acute appendicitis
   - Diverticulitis
   - Ischemic colitis
   - Radiation proctitis
   - Behcet's disease
   - Carcinoma of colon
   - Drugs—NSAIDs.

Q. What are the **causes of fistula** in abdominal wall?

A. As follows:

- Crohn's disease.
- Ileocecal tuberculosis.
- Actinomycosis.
- Disseminated malignancy.
- Trauma.

Q. What are the **differences** between ulcerative colitis and Crohn's disease?

A. As follows:

Features	Crohn's disease	Ulcerative colitis
1. Site	Mouth to anus, commonly ileum and right side of colon	Large gut, commonly rectum
2. Nature	Transmural (all layers of gut wall are involved)	Mucosa
3. Type	Patchy and discontinuous, skip lesions are present	Continuous or confluent
4. Crypt abscess	Less	Common
5. Fistula, perianal or ischiorectal abscess and skin tag	Common	Uncommon
6. Others	Deep ulcers with fissure. Mucosa in between them looks like cobblestone	Pseudopolyps (hypertrophy of mucosa)
7. Colon cancer	Less	Common
8. Microscopy - » Granuloma » Goblet cells » Cells	 » In 50 to 60% cases, non-caseating granuloma present » Slight loss or normal » Chronic inflammatory cells with lymphoid hyperplasia	 » Absent » Loss or depleted and distorted » Acute and chronic inflammatory cells in lamina propria and crypts
9. Smoking	Common in smoker	Common is nonsmoker and ex-smoker

Brief Discussion on Ulcerative Colitis

Q. What is **ulcerative colitis?**

A. It is a type of inflammatory bowel disease that involves usually the large gut, specially rectum, mainly involving the mucosa, characterized by frequent attack of bloody diarrhea.

Q. What is the **site** of involvement in ulcerative colitis?

A. Large gut commonly the rectum, which is invariably involved in 95% cases. Occasionally, terminal ileum may be involved called backwash ileitis.

Q. What is a **pseudopolyp**?

A. These are formed by swollen residual mucosa in between the areas of ulceration.

Q. What are the **types** of ulcerative colitis?

A. According to the site of involvement:

- Proctitis (when the disease is limited to rectum).
- Distal colitis (when sigmoid and descending colon are involved).
- Pancolitis or total colitis (when the whole colon is involved).

According to severity, it is divided into two types:

Points	Mild	Severe
1. Number of diarrhea	<4	>6
2. Blood in stool	Slight or no	Profuse, fresh blood
3. Pulse	<90/minute	>90/minute
4. Temperature	Normal	>37.5°C
5. Hemoglobin	Normal	<10 g%
6. ESR	Normal or <30 mm	>30 mm
7. Serum albumin	>35 g/L	<35 g/L
8. Stool volume	<200 g/day	>400 g/day
9. X-ray of abdomen	Normal	Dilated bowel with mucosal island
10. Sigmoidoscopy	Normal or granular mucosa	Blood in lumen or ulceration

Note Remember the following:

There may be a moderate type, the features for which are between mild and severe types.

Q. What are the **complications** of ulcerative colitis?

A. The complications are intestinal and extraintestinal:

1. Intestinal:
   - Perforation of colon
   - Toxic megacolon
   - Severe hemorrhage
   - Malignant change.
2. Extraintestinal—the features are similar to that for Crohn's disease (see in page 195).

Q. What is **toxic megacolon**?

A. Huge dilatation of colon with severe colitis associated with fever, tachycardia, shock and cessation of diarrhea. There is free passage of bacterial toxin through the diseased mucosa into the portal circulation. It usually occurs in the first attack of ulcerative colitis. The patient is toxic and abdomen is distended, commonly involve transverse colon. In plain X-ray, if transverse colon is > 6 cm, colonic perforation with peritonitis may occur. Barium enema is contraindicated. CT scan may be done.

Causes of toxic megacolon:

- Ulcerative colitis (common cause).
- Rarely, Crohn's disease.
- Other causes are ischemic colitis and pseudomembranous colitis.

Plain X-ray abdomen should be taken daily.

Q. How to **treat** toxic megacolon?

A. As follows:

- Nothing by mouth
- Intravenous fluid and correction of electrolytes
- Blood transfusion, if Hb <10 g%
- Hydrocortisone 100 to 200 mg 6-hourly IV or methylprednisolone IV
- Antibiotic, if infection
- Nutritional support
- If no response within 5 to 7 days, or if the condition deteriorates, surgery should be done.

Q. How to suspect **malignancy** in ulcerative colitis?

A. Extensive ulcerative colitis of more than 10 years duration is at a high risk of colorectal cancer (5% after 20 years, 12% after 25 years, 20% after 30 years). Dysplastic changes in colonic biopsy may be the early features.

Q. How will you **investigate** a case of ulcerative colitis?

A. Same as Crohn's disease.

- Barium enema—in early stage, mucosal irregularity, pseudopolyp, stricture, etc. may be seen. In chronic case, there is shortening and narrowing of the bowel with loss of haustration.
- Sigmoidoscopy—uniform continuous involvement of the mucosa, loss of mucosal vascularity, diffuse erythema, multiple ulcers, blood, mucus or pus, also there may be pseudopolyp.

Q. How to **treat** ulcerative colitis?

A. Object of treatment is—control of active disease and maintenance of remission.

Control of active disease

1. Active proctitis.
   - Oral aminosalicylate (mesalazine) plus mesalazine enema or suppository.
   - Rectal steroid (10% hydrocortisone foam or prednisolone 20 mg enema or foam) may be used.
   - If no response, then oral prednisolone 40 mg daily is administered.
2. Active left-sided or extensive proctocolitis.
   - In a mild case, oral aminosalicylate (mesalazine) plus mesalazine enema or suppository and rectal steroid.
   - In moderate to severe case, oral prednisolone 40 mg daily.
3. In severe ulcerative colitis, the patient should be hospitalised.
   - Intravenous methylprednisolone 60 mg or hydrocortisone 100 mg 6 hourly **plus** oral and topical aminosalicylate.
   - Intravenous antibiotic, if necessary.
   - General measures—intravenous fluid, blood transfusion and nutrition.
   - If no response—IV cyclosporine or infliximab may be given.
   - In patient with colonic dilatation >6 cm, or if the clinical condition deteriorates or who do not respond after 7 to 10 days with maximum conservative therapy, urgent surgery (colectomy) may be needed.
   - After recovery, oral prednisolone should be given. Once remission, it should be tapered 5 to 10 mg weekly.

Following features indicate failure of medical therapy:

- Persistent fever
- Tachycardia
- Falling hemoglobin
- Rising WBC
- Falling potassium
- Falling albumin.

Persistently raised stool volume >500 g/day with loose bloody stool:

- In such cases, surgery is indicated.

Maintenance of remission:

After recovery, oral aminosalicylate either mesalazine or balsalazide is given to prevent relapse. In chronic cases with frequent relapse or who require steroid in high dose, azathioprine (1.5 to 2 mg/kg) may be given. Cyclosporine may also help.

Note

Prednisolone is used only in active disease, it has no role to prevent relapse. 5-aminosalicylates administered are either mesalazine or olsalazine or balsalazide. Oral and enema forms are available.

Q. How to treat ulcerative colitis in **pregnancy**?

A. Pregnancy is not affected in ulcerative colitis. However, exacerbation may occur in puerperium, sometimes in first trimester of pregnancy. Drug treatment with corticosteroid, aminosalicylate or azathioprine can be continued during pregnancy.

Q. What **surgery** is done?

A. Proctocolectomy with ileostomy or proctectomy with ileoanal anastomosis is the surgical procedure done.

Indications of surgery:

1. Emergency surgery should be done in:
   - Fulminating acute active colitis, if failure of medical treatment
   - Toxic megacolon, if medical treatment fails
   - Perforation
   - Hemorrhage.
2. In chronic cases, elective surgery is done. Indications are
   - Less or no response to medical therapy
   - Frequent relapse inspite of adequate medical treatment
   - High dose steroid requirement
   - Non-compliance with drugs
   - Colonic dysplasia and suspicion of malignancy.

ILEOCECAL TUBERCULOSIS

CHIEF COMPLAINTS

- Occasional loose motion for the last … month
- Recurrent abdominal pain for … months
- Fever for … months
- Severe weakness and lethargy for … months
- Weight loss and loss of appetite for … months.

HISTORY

History of present illness: According to the statement of the patient, he was alright … months back. Since then, he has been suffering from occasional loose motion, about 5 to 6 times a day, not related to any food or drugs. Stool is moderate in amount, not mixed with fresh or altered blood. The patient also experiences recurrent colicky abdominal pain mostly around the umbilicus and also right side of the abdomen, but no radiation. It is not related to food, but relieved after defecation. He also complains of low grade continued fever for … months, with occasional peaks during evening, also associated with occasional night sweating. For the last ... months, the patient also complains of severe weakness, lethargy, loss of appetite and weight loss for the same duration. There is no history of cough, bladder abnormality or sweating.

History of past illness

Family history

Personal history

Socioeconomic history

Drug history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient is ill-looking and emaciated (also looks depressed)
- Moderately anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or no thyromegaly
- Pulse: 96/min
- BP: 120/65 mm Hg
- Temperature: 101°F
- Respiratory rate: 18/min.

SYSTEMIC EXAMINATION

Gastrointestinal System

Lips, gums, teeth, and oral cavity—normal.
Tongue—pale.

Abdomen

Inspection: No abnormality detected.

Palpation:
- Tenderness in lower abdomen, more in right iliac fossa.
- There is a small mass in the right iliac fossa, 2X2 cm in size, firm, non-terder, movable from side to side, free from overlying skin and underlying structures.
- Liver—not palpable.
- Spleen—not palpable.
- Kidneys—not ballotable.
- Succusion splash—absent.

Percussion: No abnormality detected.
Auscultation: No abnormality detected.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 36-year-old, farmer, normotensive, nondiabetic, nonsmoker, hailing from …, presented with occasional loose motion, about 5 to 6 times a day for ... months. It is not related to any food or drugs. Stool is moderate in amount, not mixed with fresh or altered blood. The patient also experiences recurrent colicky abdominal pain mostly around the umbilicus and also right side of the abdomen, but no radiation. It is not related to food, but relieved after defecation. He also complains of low grade continued fever for … months, with occasional peaks during evening, also associated with occasional night sweating. For the last ... months, the patient also complains of severe weakness, lethargy, loss of appetite and weight loss for the same duration. There is no history of cough, bladder abnormality or sweating. He used to take paracetamol, vitamins, antacid, ranitidine, etc. prescribed by local physicians. There is no history of such illness in his family.

On examination – general examination (mention as above).

Systemic examination (mention as above).

With the above history and physical findings, I have some differential diagnoses
- Ileocecal tuberculosis
- Crohn's disease
- Lymphoma
- Carcinoma of cecum (in elderly).

Q. What are the **causes** of mass in right iliac fossa?

A. As follows:

1. If the patient is young:
   - Appendicular lump (tender)
   - Ileocecal tuberculosis
   - Crohn's disease
   - Lymphoma
   - Ameboma (less common nowadays, because of wide use of metronidazole)
   - Others—actinomycosis, Yersinia, tubo-ovarian mass in female, pelvic kidney.
2. If the patient is elderly or middle aged:
   - Appendicular lump (tender)
   - Ileocecal TB
   - Carcinoma of cecum (hard, irregular and nontender)
   - Lymphoma
   - Others—as above.

Note Remember the following:

If there is scar mark in lumbar area, diagnosis is transplanted kidney.

Q. Mention one **single investigation** which will be helpful for the diagnosis.

A. Ultrasonogram of whole abdomen.

Q. What **investigations** do you suggest?

A. As follows:

- CBC with ESR
- Ultrasonogram of whole abdomen
- X-ray chest (shows TB in 50%)
- MT
- Colonoscopy with ileoscopy
- Barium follow through with spot film in ileocecal region
- CT scan of abdomen
- Laparoscopy to see tubercle in peritoneum and biopsy.

RELATED QUESTIONS AND ANSWERS

Q. What are the **causes** of ileocecal tuberculosis? (What is the **pathogenesis**?)

A. It is caused by reactivation of primary disease by *Mycobacterium tuberculosis*. May be secondary to pulmonary TB (by swallowing of sputum). Sometimes, primary TB due to Mycobacterium bovis (rare nowadays). After involvement of mucosa and submucosa, intense inflammation with necrosis occurs in the bowel wall and lymphatic. Caseation is often found.

Q. What is the **type of lesion** and **type of ulcer** in ileocecal tuberculosis?

A. Types of lesion—ulcerative, hypertrophic or mixed. Ulcer is transverse (in typhoid and Crohn's disease, the ulcer is longitudinal).

Q. What are the **presentations** of ileocecal TB?

A. History of pulmonary TB may be present. Other features are:

- Abdominal pain is the commonest (usually in right iliac fossa, occasionally generalized), colicky in nature.
- Features of intestinal obstruction (acute or subacute), or peritonitis or ascites.
- Diarrhea or malabsorption syndrome.
- Mass in right iliac fossa.
- Others are fever, malaise, loss of weight and fistula formation.

Q. What are the **complications** of ileocecal tuberculosis?

A. As follows:

- Intestinal obstruction
- Fistula (entero-enteric or entero-cutaneous)
- Malabsorption
- Perforation (rare).

Q. How to **treat** ileocecal TB?

A. As follows:

- Standard anti-TB chemotherapy (using four drugs) for one year.
  Occasionally, surgery (if intestinal obstruction or fistula).

CARCINOMA OF COLON

CHIEF COMPLAINTS

- Pain in left lower abdomen for … months
- Constipation for … months
- Occasional bleeding per rectum for … days
- Weight loss for … months.

HISTORY

History of present illness: According to the patient, he was reasonably well … months ago. Since then, he has been suffering from occasional pain in the left lower abdomen. The pain is colicky, localized, associated with constipation and relieved by bowel movement. It has no relation to food or empty stomach. He denies any history of vomiting, hematemesis or melena. Stool is semisolid or sometimes hard in consistency and very often mixed with fresh blood. The patient also complains of marked loss of appetite and significant weight loss over the last … months. There is no history of fever, excessive sweating, polyuria or diarrhea.

History of past illness

Family history

Personal history

Socioeconomic history

Drug history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient is ill-looking and emaciated
- Moderately anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- Pulse: 100/min
- BP: 110/70 mm Hg
- Temperature: 98ºF
- Respiratory rate: 18/min.

SYSTEMIC EXAMINATION

Gastrointestinal System

Lips, gums, teeth, and oral cavity—normal.
Tongue—pale.

Abdomen

Inspection: No abnormality detected.
Palpation:

- There is a mass in left iliac fossa, 3 × 4 cm, non-tender, firm in consistency, surface is irregular, margin is irregular and it is immobile.

- Liver—enlarged, ... cm from the costal margin in right midclavicular line. Margin is round, surface is irregular and nodular, nontender, hard in consistency. Upper border of liver dullness in ... intercostal space in right midclavicular line. There is no hepatic bruit.
- Spleen—not palpable.
- Kidneys—not ballotable.
- Succusion splash—absent.

Percussion: No abnormality detected.
Auscultation: No abnormality detected.

Digital rectal examination (DRE): No abnormality.
Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 70-year-old, retired policeman, normotensive, nondiabetic, nonsmoker, hailing from …, presented with occasional pain in the left lower abdomen for … months. The pain is colicky, localized, associated with constipation and relieved by bowel movement. It has no relation to food or empty stomach. He denies any history of vomiting, hematemesis or melena. Stool is semisolid or sometimes hard in consistency and very often mixed with fresh blood. The patient also complains of marked loss of appetite and significant weight loss over the last … months. There is no history of fever, excessive sweating, polyuria or diarrhea. There is no such illness in his family. He used to take some vitamins and pain killers.

On examination—general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is carcinoma colon with hepatic metastasis.

Q. What is your **differential diagnosis?**

A. As follows:
- Lymphoma.

Q. What **investigations** do you suggest in colorectal carcinoma?

A. As follows:
- USG of whole abdomen (to see the mass, metastases, lymph node involvement).
- Sigmoidoscopy or colonoscopy and biopsy (gold standard).
- CT colonography.
- CT scan of whole abdomen.
- Endoanal ultrasound or pelvic MRI (used for staging of rectal cancer).
- PET scan is useful for detecting occult metastases and for evaluation of suspicious lesions found on CT or MRI.
- Barium enema (double contrast)—may be helpful to see the mass, but CT colonography is more preferable.
- Others—complete blood count, stool for occult blood, CEA (to see recurrence), X-ray chest.
- FNAC (CT guided or USG guided).
- Sometimes, laparotomy may be needed.

Q. What are the **causes** of mass in left iliac fossa?

A. Mention according to the age of the patient:

If the patient is young, the causes are:
- Thick colon (in irritable bowel syndrome).

- Fecal mass (mass indented and moulded by pressure).
- Occasionally, normal colon may be palpable (mainly in lean and thin person).
- Carcinoma of colon (rare).
- Diverticulitis.
- Tubo-ovarian mass in female.
- Pelvic kidney.
- (If laparotomy scar is present, the diagnosis is transplanted kidney. Examine for AV fistula and anemia).

If the patient is elderly the causes are

- Carcinoma of colon (descending or sigmoid colon).
- Diverticulitis (tender, mobile mass).
- Fecal mass.
- (If laparotomy scar is present, the diagnosis is transplanted kidney. Examine for AV fistula and anemia).

Note Remember the following:

- Carcinoma may be in the cecum, transverse colon, etc. In this case, there may be mass in the right iliac fossa.

RELATED QUESTION OF COLORECTAL CARCINOMA

Q. What are the **sites** of colorectal carcinoma?

A. As follows:

- Rectum (20%)
- Rectosigmoid (10%)
- Sigmoid colon (25%)
- Cecum and ascending colon (25%)
- Transverse colon (15%)
- Descending colon (5%).

Q. What is the **most common site** of carcinoma of colon?

A. Rectosigmoid (65% cases) is the most common site.

Q. What are the **types** of carcinoma of colon?

A. As follows:

1. Macroscopically:
   - Polypoid and fungating
   - Annular and constricting.
2. Microscopically: Adenocarcinoma.

Q. What are the **causes** or **predisposing factors** for carcinoma of colon?

A. The causes are unknown. Predisposing factors are as follows:

3. Dietary factors:
   - Excess consumption of red meat, saturated animal fat.
   - Less dietary fibers.
   - Less intake of vegetables and fruits (high vegetables and fruits may be preventive for carcinoma).
   - Excess and prolonged sugar consumption.

4. Non-dietary factors:
   - Increasing age.
   - Genetic factors such as benign adenomatous polyp or familial adenomatous polyposis.
   - Hereditary non-polyposis colonic cancer.
   - Family history of colon cancer.
   - Long-standing extensive ulcerative colitis or Crohn's colitis, especially if associated with primary sclerosing cholangitis.
   - Personal history of breast cancer.
   - Ureterosigmoidostomy.
   - Acromegaly.
   - Pelvic radiotherapy.
   - Alcohol (weak association)
   - Smoking (relative risk 1.5 to 3.0).
   - Obesity and sedentary lifestyle.
   - Cholecystectomy.
   - Type 2 diabetes (hyperinsulinemia).

Factors which decrease risk of colorectal carcinoma:

- Diet—Increased fiber, fruits, vegetable, garlic, milk.
- Exercise (colon only).
- Drugs—Aspirin or other NSAIDs, calcium, folic acid, omega 3 fatty acids, combined estrogen and progesterone hormone replacement therapy.

Q. What are the **features** of carcinoma of colon?

A. The features of carcinoma of colon depend on the site (may be asymptomatic)

- If on the left side, there may be bleeding per rectum, alteration of bowel habit, mass in left iliac fossa.
- If on the right side, there may be alteration of bowel habit, intestinal obstruction, mass in right iliac fossa.

Note Remember the following:

Any patient over 35 to 40 years of age presenting with new large bowel symptoms should be investigated. Alarming symptoms are change in bowel habit, rectal bleeding, anorexia and weight loss, fecal incontinence, tenesmus and passing mucus per rectum.

Q. How **screening and prevention** are done in carcinoma of colon?

A. Screening is done as follows:

- Any person >50 years of age, stool is tested for the presence of occult blood.
- Colonoscopy (gold standard).
- Flexible sigmoidoscopy is an alternative to colonoscopy.
- CT colonoscopy may be used in screening program.
- Screening for high risk patients by molecular genetic analysis (very promising, but not widely available).

Prevention:

- Chemoprevention by using aspirin, calcium, folic acid. Cox 2 inhibitor may have some role to play in prevention.
- Secondary prevention to detect early and precancer stage. It is done by screening.

Note Remember the following:

- Colorectal carcinoma is common in the western world, less among Asians
- Second common cause of death.

Q. How the colorectal carcinoma **spreads**?

A. As follows:

- Local infiltration through bowel wall
- By lymphatics
- By blood
- Transcoelomic.

Q. How to **treat** colorectal carcinoma?

A. Depends upon the stages of the cancer

1. Curative:
   - Surgical resection of the tumor with removal of pericolic lymph nodes.
   - Adjuvant postoperative chemotherapy (with 5 fluorouracil and folinic acid).
   - Radiotherapy is not much helpful. Preoperative radiotherapy may be given to large fixed rectal cancer to make it resectable. Postoperative radiotherapy may be required in some cases.
   - In some cases with metastatic disease, monoclonal antibody like bevacizumab or cituximab either alone or with chemotherapeutic agents, such as irinotecan may be used.
2. Palliative:
   - Palliative chemotherapy with 5FU may improve survival. If this fails, second line drug such as irinotecan may be given.
   - Endoscopic laser therapy or insertion of an expandable metal stent can be used to relieve obstruction.

READ THE FOLLOWING

Q. What are the causes of **epigastric mass**?

A. Mention according to the age of the patient.

If the patient is middle aged or elderly, the causes are:

1. Mass in left lobe of liver (hepatoma, secondaries and hydatid cyst).
2. Carcinoma of stomach.
3. Lymphoma of stomach.
4. Carcinoma of head of the pancreas.
5. Others:
   - Tender mass (liver abscess)
   - Soft and cystic mass (pancreatic pseudocyst)
   - Mass in transverse colon (carcinoma)
   - Pulsating mass (aneurysm of abdominal aorta)
   - Epigastric hernia.

If the patient is young, causes are:

- Lymphoma of stomach
- Mass in left lobe of liver (hydatid cyst and hepatoma. If tender mass, it may be liver abscess)
- Epigastric hernia
- Pancreatic pseudocyst.

Q. What are the causes of mass in **right iliac fossa**?

A. Tell the causes according to the age of the patient.

If the patient is young:

1. Appendicular lump (tender)
2. Ileocecal TB
3. Crohn's disease
4. Lymphoma
5. Ameboma (less common nowadays, because of wide use of metronidazole)
6. Others:
   - Actinomycosis, Yersinia infection
   - Tubo-ovarian mass in female
   - Pelvic kidney.

If the patient is elderly or middle aged:

- Appendicular lump (tender)
- Ileocecal TB
- Carcinoma of cecum (it is hard, irregular and non-tender)
- Lymphoma
- Others may be as above.

Note Remember the following:

If there is scar mark in lumbar area, diagnosis is transplanted kidney.

Q. What are the causes of **unilateral renal mass?**

A. As follows:

- Renal cell carcinoma (in elderly) or Wilms' tumor (in children)
- Unilateral hydronephrosis or pyonephrosis
- Hypertrophied single kidney (if nephrectomy of other kidney or congenital absence of one kidney).
- Renal cyst
- Polycystic kidney with single palpable kidney (due to asymmetrical enlargement).

Note Remember the following:

Right kidney may be normally palpable.

Q. What are the causes of **bilateral renal mass**?

A. As follows:

- Polycystic kidney disease
- Bilateral hydronephrosis
- Diabetic nephropathy in early stage
- Amyloidosis
- Rarely, bilateral renal cell carcinoma.

Q. What are the causes of mass in **right hypochondrium?**

A. As follows:

- Mass in liver (hepatoma, secondaries and hydatid cyst)
- Gall bladder mass (carcinoma, mucocele or empyema of gallbladder)
- Mass in right side of colon (malignancy)
- Carcinoma head of pancreas.

Q. What are the causes of mass in **central abdomen** (other than epigastric mass)**?**

A. According to the age and sex, the causes are as follows:

If the patient is young or early aged, the causes are:

- Lymphoma
- Tuberculosis (tabes mesentericus or lymphadenitis)
- Hydatid cyst
- Mesenteric cyst
- In female, ovarian cyst, pregnancy
- Distended urinary bladder (urinary retention).

If the patient is elderly or middle aged, the causes are:

- Intra-abdominal malignancy
- TB (tabes mesentericus or lymphadenitis)
- Lymphoma
- Metastatic lymphadenitis
- Hydatid cyst
- Mesenteric cyst
- Retro-peritoneal growth (sarcoma)
- Distended urinary bladder (urinary retention).

CHAPTER 5

Hepatobiliary System

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OBSTRUCTIVE JAUNDICE

CHIEF COMPLAINTS

- Yellow discoloration of urine and eyes for … months
- Itching of whole body for … months
- Anorexia and weight loss for … months

HISTORY

History of present illness: The patient states that he was completely alright about … months back. Since then, he noticed yellow discoloration of his urine, eyes and whole body, which is gradually increasing. Initially jaundice is not associated with any nausea, loss of appetite or vomiting (which are prodrome of acute viral hepatitis). His stool is clay colored, voluminous, associated with mucus but no blood. He also complains of generalized itching that is more marked during the night and interferes with sleeping. For the last … months, the patient also complains of anorexia and marked loss of weight, about 10 kg. He does not complain of fever or abdominal pain or swelling of the body and leg.

History of past illness: There is no previous history jaundice, injection, infusion or blood transfusion, dental extraction, sharing of needles, colicky abdominal pain or abdominal surgery.

Personal history: He is a clerk, nonsmoker, nonalcoholic.

Family history: Nothing significant.

Drug and treatment history: Mention according to the patient's statement.

GENERAL EXAMINATION

- Ill looking
- Deeply jaundiced and mildly anemic
- No cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- There are multiple scratch marks all over the body, more marked over the extensor surfaces of upper and lower limbs
- No stigmata of chronic liver disease
- Bony tenderness—absent
- Flapping tremor—absent.

SYSTEMIC EXAMINATION

Gastrointestinal System

- Lips, gums, teeth normal
- Tongue and oral cavity—yellowish.

Abdomen

Inspection: Normal.

Palpation:

- Liver is palpable, 10 cm from the right costal margin in the mid-clavicular line, margin is sharp, surface is smooth, firm in consistency and nontender. Upper border of the liver dullness is in the right 4th intercostal space, in midclavicular line. There is no bruit.
- Spleen—not palpable.
- Kidneys—not ballotable.
- Testes—normal.

Percussion: Normal.

Auscultation: No abnormality detected.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 44 years old, a clerk, normotensive, nondiabetic, nonsmoker, nonalcoholic, hailing from …, presented with yellow discoloration of his urine, eyes and whole body, which is gradually increasing. Initailly jaundice is not associated with any nausea, loss of appetite or vomiting (which are prodrome of acute viral hepatitis). His stool is clay colored, voluminous, associated with mucous but no blood. He also complains of generalized itching, which is more marked during the night and interferes with sleeping. For the last … months, the patient also complains of anorexia and marked loss of weight, about 10 kg. He does not complain of fever or abdominal pain or swelling of the body and leg.

There is no previous history jaundice, injection, infusion or blood transfusion, dental extraction, sharing of needles, colicky abdominal pain or abdominal surgery. There is no history of intravenous drug abuse. There is no family history of similar illness. He used to take ranitidine and painkillers.

On examination – general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is obstructive jaundice which may be due to:

- Carcinoma head of the pancreas
- Stone in the common bile duct
- Periampullary carcinoma
- Cholangiocarcinoma.

Q. Mention one **single** investigation that is helpful for your diagnosis.

A. Ultrasonography of abdomen.

Q. Why it is obstructive jaundice?

A. Because:

- The stool is pale or clay colored with steatorrhea
- Generalized itching with scratch mark
- Deep and progressively increasing jaundice.

Q. Can these features occur in viral hepatitis?

A. Obstructive features may occur in viral hepatitis due to intrahepatic cholestasis, which recovers completely after acute stage is over.

Q. What other **investigations** do you suggest?

A. As follows:

- CBC.

- Liver function tests—Serum bilirubin, SGPT, alkaline phosphatase (very high), γ glutamyl transferase (very high), prothrombin time, serum total protein and A : G ratio.
- CA 19–9 (high in carcinoma of pancreas).
- USG of hepatobiliary system and pancreas.
- Viral markers (HBsAg, Anti-HBc IgG, HBeAg, Anti-HCV).
- CT scan or MRI of upper abdomen.
- MRCP or ERCP.

Q. What are the **features** of obstructive jaundice?

A. As follows:

1. Early features:
   - Deep jaundice, dark yellow skin, deep yellow or mustard oil like urine.
   - Pale or clay colored stool.
   - Generalized itching with scratch mark.
   - Palpable gallbladder may be present (obstruction due to carcinoma of the head of the pancreas).
   - Deep seated abdominal pain due to stone in the common bile duct (choledocholithiasis), pancreatitis, choledochal cyst, sometimes due to carcinoma head of the pancreas.
2. Late features:
   - Malabsorption leading to weight loss, steatorrhea, osteomalacia due to vitamin D deficiency, bleeding disorder due to vitamin K deficiency, night blindness due to vitamin A deficiency (all are due to lack of bile salts).
   - Xanthoma, xanthelasma may be present.
   - There may be cholangitis due to secondary infection. Features of cholangitis are jaundice, right upper quadrant pain and fever (Charcot's triad).

Q. Why there is **bleeding tendency** in obstructive jaundice?

A. Due to vitamin K deficiency, which is due to lack of bile salts. So, vitamin K dependent factors such as factor II, VII, IX, X will be deficient, leading to bleeding. Prothrombin time will be prolonged. In such case, vitamin K therapy is helpful, should be given parenterally.

Q. What are the features of **hepatocellular jaundice?**

A. As follows:

- Prodromal syndrome like anorexia, nausea and vomiting
- Orange yellow tinge of the bulbar conjunctiva
- Yellowish urine
- High colored stool (may become pale if there is intrahepatic cholestasis. Pruritus is present)
- Tender hepatomegaly
- Disproportionate rise in the aminotransferases compared to the alkaline phosphatase
- There may be bleeding manifestations as a result of hepatocellular failure.

Q. What are the features of **hemolytic jaundice?**

A. As follows:

- Triad of jaundice, anemia and splenomegaly. Jaundice is usually mild, serum bilirubin is usually < 6 mg/dL. Bilirubin is predominantly of unconjugated variety (SGPT, SGOP, gamma GT, alkaline phosphatase, all are normal).
- Liver may be mildly enlarged, not tender.
- Pale lemon complexion.
- If hemolysis is due to hemoglobinopathy, the jaundice is persistent for a long time. There may be Mongoloid faces (frontal and parietal bossing, prominent malar bones), short stature, leg ulcer.
- Acholuric urine.

- High colored stool due to excess amount of stercobilinogen and stercobilin.
- Reticulocytosis in peripheral blood.

Q. What are the causes of **mass in right hypochondrium?**

A. As follows:

- Hepatic mass, such as hepatocellar carcinoma, secondaries and hydatid cyst.
- Gall bladder mass such as carcinoma, mucocele or empyema of gallbladder.
- Mass in right side of colon, such as carcinoma of the ascending colon, also in hepatic flexure.
- Carcinoma of the head of the pancreas.

RELATED QUESTIONS AND ANSWERS

Q. What are the **causes** of obstructive jaundice?

A. Obstruction usually occurs in common bile duct. The causes may be in the lumen, in the wall and outside the wall of CBD.

1. Causes in the lumen:
   - Stone in CBD (choledocholithiasis)
   - Worms (ascariasis).
2. Causes in the wall:
   - Sclerosing cholangitis
   - Cholangiocarcinoma
   - Periampulary carcinoma
   - Stricture (may be following surgery, trauma).
3. Causes outside the wall:
   - Carcinoma head of the pancreas
   - Lymphoma
   - Enlargement of the lymph node in porta hepatis.

Q. What are the **intrahepatic causes** of cholestatic (obstructive) jaundice?

A. As follows:

- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Viral hepatitis (especially HEV)
- Drugs and alcohol
- Autoimmune hepatitis
- Cystic fibrosis
- Postoperative
- Benign recurrent intrahepatic cholestasis
- Pregnancy.

Q. What are the causes of **fluctuating jaundice?**

A. As follows:

- Choledocholithiasis
- Choledochal cyst
- Sometimes in primary sclerosing cholangitis
- Hemolytic jaundice
- Wilson disease
- Gilbert's syndrome
- Benign recurrent intrahepatic cholestasis (BRIC)
- Recurrent pancreatitis.

Q. What are the causes of **progressive jaundice?**

A. As follows:

- Carcinoma of the head of the pancreas
- Cholangiocarcinoma
- Primary biliary cirrhosis
- Primary sclerosing cholangitis.

Q. What are the causes of **palpable gallbladder with jaundice?**

A. As follows:

- Carcinoma of head of pancreas
- Carcinoma of ampulla of Vater
- Stone in common bile duct
- Pressure from outside on bile duct (lymphoma and secondaries)
- Cholangiocarcinoma
- Sclerosing cholangitis.

Q. What are the causes of **palpable gallbladder without jaundice?**

A. As follows:

- Mucocele
- Empyema
- Occasionally, carcinoma of the gallbladder.

Q. Could it be **gall stone** with palpable gallbladder?

A. Unlikely (but gallbladder is palpable, if the stone is in common bile duct).

Uncommon but possible if there is double impaction, i.e. one stone in cystic duct and one stone in distal CBD.

Q. What is **Courvoisier's law?**

A. It is as follows:

- In a jaundiced patient with palpable gallbladder, the cause is unlikely to be gallstones, rather it is due to carcinoma head of pancreas and extrinsic pressure in bile duct.

Reverse of the law:

- Obstructive jaundice without palpable gallbladder is unlikely to be carcinoma head of pancreas and extrinsic pressure in common bile duct.

Q. Why gallbladder is **not palpable** in gallstone disease?

A. Gallstone is associated with chronic cholecystitis and gallbladder is fibrosed, which is unable to enlarge.

Q. What are the **congenital nonhemolytic hyperbilirubinemia?**

A. As follows:

1. Gilbert's syndrome (unconjugated hyperbilirubinemia)
2. Crigler-Najjar syndrome (unconjugated hyperbilirubinemia)
3. Dubin-Johnson syndrome (conjugated hyperbilirubinaemia)
4. Rotor's syndrome (conjugated hyperbilirubinemia).

Gilbert's syndrome:

- It is inherited as autosomal dominant. There is reduction of glucuronyl transferase and abnormality in uptake of bilirubin.
- Mild jaundice, especially with fasting.
- No treatment is necessary, only reassurance is sufficient.

Crigler-Najjar syndrome

- There are two types:
- Type I is inherited as autosomal recessive. There is absence of glucuronyl transferase, the patient dies in neonatal period due to kernicterus.
- Type II is inherited as autosomal dominant. There is reduction of glucuronyl transferase. The patient usually survives up to adulthood. Treatment is by phenobarbitone, ultraviolet light or liver transplantation.

Dubin-Johnson syndrome:

- It is inherited as autosomal recessive. There is defect in excretion of bilirubin.
- Usually mild disease.
- Liver is black due to deposition of lipofuscin and melanin.
- Urinary coproporphyrin I is increased.
- No treatment is necessary.

Rotor's syndrome:

- It is inherited as autosomal recessive. There is defect in uptake and conjugation bilirubin in the liver.
- Mild disease.
- Urinary total coproporphyrin is increased.
- No treatment is necessary.

ACUTE VIRAL HEPATITIS

CHIEF COMPLAINTS

- Loss of appetite, nausea and vomiting for … days
- Yellow coloration of urine and eyes for … days.
- Pain and discomfort in the upper abdomen for the same duration
- General weakness for … days

HISTORY

History of present illness: The patient states that, she was alright about … days back. Since then, she has been suffering from malaise, loss of appetite, nausea and vomiting. The vomitus is bile-stained with some food residue, but no blood. She also noticed gradually increasing yellow coloration of her urine and eyes for the same duration. Her stool is yellowish and not voluminous and not clay colored. There is no history of itching. The patient also complains of pain and discomfort in the right upper abdomen. It is not related to food and there is no radiation to the shoulder. She also complains of general weakness for the same duration. There is no history of fever, skin rash, contact with jaundice patient, intake of drugs, injection, infusion, blood transfusion or IV drug abuse, travel history or sexual exposure.

History of past illness: Mention according to the patient's statement.

Personal history: Mention according to the patient's statement.

Family history: There is no history of such illness in her family.

Drug and treatment history: She is on oral contraceptives, but takes no other medicine related to her symptoms.

Menstrual history: It is regular. Her LMP was 10 days ago.

GENERAL EXAMINATION

- The patient is ill looking
- There is moderate jaundice
- No cyanosis, clubbing, koilonychia, leukonychia or edema, spider angioma or palmar erythema Flapping tremor is absent
- No lymphadenopathy or thyromegaly
- No skin rash
- Pulse—68/min
- BP—110/70 mm Hg
- Respirator`y rates—20/min
- Temperature—100°F.

SYSTEMIC EXAMINATION

Gastrointestinal System

- Lips, gums, teeth—normal
- Under surface of tongue and oral cavity—yellowish.

Abdomen

Inspection: No abnormality detected.

Palpation:

- Liver is palpable, 3 cm from the right costal margin in the mid-clavicular line, margin is sharp, surface is smooth, soft in consistency, and tender. Upper border of liver dullness is in the right 5th intercostal space along the midclavicular line. There is no hepatic bruit.
- Spleen is not palpable.
- Kidneys are not ballotable.
- Ascitis is absent as evidenced by absent shifting dullness and fluid thrill.

Percussion: No abnormality detected.

Auscultation: No abnormality detected.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mrs. …, 33 years old, housewife, normotensive, nondiabetic, nonsmoker, nonalcoholic, hailing from …, presented with malaise, loss of appetite, nausea and vomiting for … days. The vomitus is bile stained with some food residue, but no blood. She also noticed gradually increasing yellow coloration of her urine and eyes for the same duration. Her stool is yellowish and not voluminous and not clay colored. There is no history of itching. The patient also complains of pain and discomfort in the right upper abdomen. It is not related to food and there is no radiation to the shoulder. She also complains of general weakness for the same duration. There is no history of fever, skin rash, contact with jaundice patient, intake of drugs, injection, infusion, blood transfusion or I/V drug abuse, travel history or sexual exposure. There is no history of such illness in her family. She is on oral contraceptives, but takes no other medicine related to her symptoms. Her LMP was 10 days ago.

On examination – general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is acute viral hepatitis

Q. What are your **differential diagnoses?**

A. As follows:

- Obstructive jaundice
- Hemolytic jaundice
- Weil's disease.

Q. Why is this not **obstructive jaundice?**

A. Because, there is no feature of obstructive jaundice, such as – no itching, scratch mark or shiny nails and no clay colored stool. Also in obstructive jaundice, there is deep jaundice, dark yellow skin and deep yellow or mustard oil like urine, which are not present in this case.

Q. Why not **hemolytic jaundice?**

A. Because, in case of hemolytic anemia, usually there are triad of anemia, jaundice and splenomegaly. Also, there is long history of jaundice, but no anorexia, nausea or vomiting. If hemolytic jaundice is due to hemoglobinopathy, there may be bony changes like frontal and parietal bosing, prominent malar bones (Mongoloid facies).

Q. What **investigations** do you suggest in acute viral hepatitis?

A. As follows:

1. CBC (there may be leukopenia, with relative lymphocytosis).
2. Liver function tests:
   - Serum bilirubin—high.
   - SGPT—high.
   - SGOT – may be high (SGOT is more raised in drug-induced hepatitis).
   - Alkaline phosphatase may be high (rarely more than twice the upper limit. In cholestatic hepatitis, alkaline phosphatase may be very high).
   - Prothrombin time – prolonged in severe hepatitis.
3. Viral markers:
   - Virus A (anti-HAV, IgM indicates acute infection).
   - Virus B (HBsAg, HBeAg, anti-HBc). In acute infection, HBsAg may be cleared rapidly; anti-HBc IgM is diagnostic.
   - Virus E (anti-HEV, IgM indicates acute infection), anti-HCV.
4. USG of hepatobiliary system.
5. Others—Blood sugar, urine R/E.

Note Remember the following points:

- HBsAg appears in the blood 6 weeks to 3 months after acute infection, then disappears.
- HBeAg rises early and declines rapidly.
- Anti-HBc is the first antibody to appear and high titers of IgM anti-HBc suggest acute infection and continuing viral replication. It persists for many months.
- Anti-HBsAg appears late and indicates immunity.
- Anti-HBe appears after anti-HBc. Its appearance indicates decreased infectivity.

Q. What are the **markers** of HBV infection?

A. As follows:

- HBsAg (it may persist for few days, but usually 3 to 4 weeks, can persist up to 5 months. But if it persists > 6 months, indicates chronic infection).
- HBeAg (indicates active replication. If it persists for > 6 month, indicates chronic infection).
- Anti-HBc (IgM type indicates acute infection).
- HBV DNA (by PCR).

Q. What are the **markers** of B virus replication?

A. HBeAg, HBV-DNA.

RELATED QUESTIONS AND ANSWERS

Q. What are the causes of **acute hepatitis?**

A. As follows:

- Acute viral hepatitis (see below).
- Drugs – paracetamol, alcohol.
- Nonviral infection—Toxoplasma gondii, Leptospira icterohaemorrhagiae, Coxiella burnetii (Q fever).
- Others—pregnancy, Wilson's disease, poisons (amanita phyllodes mashroom, aflatoxin, carbon tetrachloride).

Q. What are the causes of **chronic hepatitis?**

A. As follows:

- Virus—HBV, HCV, combined HBV and HDV
- Autoimmune
- Drugs—methyldopa, isoniazid, ketoconazole, nitrofurantoin
- Alcohol
- Hereditary—Wilson's disease, hemochromatosis, α_1 antitrypsin deficiency
- Inflammatory bowel disease (Ulcerative colitis).

Q. What are the **viruses** causing hepatitis?

A. As follows:

- Hepatitis A, B, C, D and E virus.
- Other viruses are Epstein-Barr virus, CMV, herpes simplex virus and yellow fever virus.

Note Remember the following:

D virus is a RNA-defective virus, can infect only with B virus or can superinfect in those who are HBV carriers. Only B virus is DNA type, and all others are RNA type.

Q. What **history** should be taken in acute viral hepatitis?

A. As follows:

1. Anorexia, nausea and vomiting.
2. Pain (usually in right hypochondrium).
3. High-colored urine, yellow eye and body.
4. Later on (due to intrahepatic cholestasis), there may be itching, pale stool.
5. History specific for HBV:
   - Injection or infusion of blood and blood products, any fluid
   - Injection of contaminated needle or sharing of syringe by others or parenteral drug abusers
   - Acupuncture or tattooing
   - Sexual contact with infected person
   - Homosexuality
   - Organ transplantation
   - Chronic hemodialysis
   - Travel to other parts
   - Newborn in infected mother with HBV.

Note Remember the following:

Clinical features and pathological features are same in all viruses causing hepatitis. They differ in their tendency to cause acute and chronic infections. HBV and HCV may cause chronic hepatitis. HDV can cause chronic infection with HBV. HAV and HEV are not associated with chronic infection.

Q. What are the **complications** of acute viral hepatitis?

A. As follows:

- Acute fulminating hepatic failure (by B and sometimes with E viral infection in pregnancy. It is rare by HAV).
- Relapsing hepatitis. It may be clinically evident (5 to 15%) or, more commonly, only biochemically detectable. It settles spontaneously.
- Cholestatic hepatitis mostly by HAV, may persist for 7 to 20 weeks.

- Post-hepatitis syndrome: It is seen in anxious patient who complain of malaise, anorexia, nausea, vomiting, right hypochondrial pain or discomfort in the absence of clinical or biochemical evidence of liver disease. Reassurance is necessary.
- Chronic liver disease (due to B and C virus), which may lead to cirrhosis of liver and ultimately to hepatoma.
- Others: Aplastic anemia (usually reversible), rarely Coomb's positive hemolytic anemia, polyarteritis nodosa, Henoch-Schönlein purpura, glomerulonephritis and collagen vascular disease.

Q. How would you **treat** a patient with acute viral hepatitis?

A. As follows:

- Bed rest
- Normal diet
- Supportive and symptomatic
- Avoid sedative, opium and alcohol.

Note Remember the following:

Bed rest and extra dietary measures are unhelpful.

Q. What is the **prognosis** of acute viral hepatitis?

A. It depends on the type of the virus:

1. HAV:
   - Good, recovery in 3 to 6 weeks
   - Rarely (0.1%) develop acute liver failure
   - Mortality in young adult is 0.1% from acute fulminating hepatic failure. Mortality increases with age.
2. HBV:
   - In 90 to 95% cases, full recovery occurs within 6 months.
   - 5 to 10% develop chronic infection which usually continues for life. Many may remain as inactive HBV infection. In some cases, cirrhosis of the liver and hepatoma may develop after many years. Cirrhosis usually develops in 5 to 20% cases in 5 to 20 years. This proportion is higher in those with HBeAg positive.
   - < 1% may develop fulminating hepatic failure.
   - Infection from mother to child during pregnancy leads to chronic infection in child in 90% case and recovery is rare.
   - Chronic infection is also common in Down's syndrome and HIV infection.
3. HCV:
   - Rarely causes acute infection
   - Commonly it causes chronic hepatitis.
4. Combined HBV and HDV infection can cause more aggressive disease.
5. HEV:
   - Similar to HAV
   - Can cause acute liver failure with high mortality in pregnancy.

Features of Different Virus Causing Hepatitis

Hepatitis A virus (HAV):

- It is a picorna group of enterovirus (RNA virus).

- Highly infectious, spread by feco-oral route.
- Infection is common in children, mostly remain asymptomatic.
- Infection is common in overcrowding and poor sanitation.
- No chronic carrier.

Hepatitis B virus (HBV):

- It is a hepadna group of DNA virus.
- Humans are the only source of infection.
- Mode of infection:
  - Vertical transmission from mother to child in the perinatal period is the commonest mode of infection worldwide (90% cases). It is not transmitted by breastfeeding.
  - Horizontal transmission by injection, transfusion, sexual exposure, etc. occurs only in 10% cases. Virus can be found in semen and saliva. In children, it may be transmitted by minor abrasion, close contact with other children, etc. But it usually does not spread in feco-oral route.
- Features of acute infection are same as in any viral infection. But certain extra features may be present such as serum sickness like illness characterized by skin rash (urticaria or maculopapular rash), polyarthritis affecting small joints, fever, extrahepatic immune complex mediated arteritis or glomerulonephritis.
- There is no definite role of antiviral drug in acute infection. But antiviral drugs may be needed in chronic HBV infection (see below).
- Neonates born of hepatitis B infected mother should be immunized at birth and immunoglobulin is given. HBV serology should be checked at 12 months of age.

Q. How to **treat** chronic HBV infection?

A. As follows:

1. In chronic hepatitis B infection, no drug is available to eradicate the infection completely (that is render the patient HBsAg negative). However, drug treatment is given to:
   - Make HBeAg seroconversion
   - Reduction of HBV-DNA
   - Normalization of liver function tests.
2. Indication of drug treatment are—patient with high viral load, HBeAg positive, high ALT and histological evidence of inflammation and fibrosis should be treated.
   - The patient with positive HBeAg, HBsAg and HBV-DNA > 20000 IU/mL, with ALT > 2 times of normal – should be treated. Liver biopsy is not essential in this group.
   - Similar patient with HBV-DNA > 20000 IU/mL, but with ALT < 2 times of normal – should not be treated as efficacy is less. If liver biopsy shows inflammation, then the patient may be treated.
   - The patient with negative HBeAg with HBV-DNA > 20,000 IU/mL – should also be treated.
   - The patient with compensated cirrhosis with HBV-DNA > 2,000 IU/ml or patient with compensated cirrhosis with HBV-DNA < 2,000 IU/mL, but high ALT – should be treated.
   - The patient with decompensated cirrhosis can be treated, but liver transplantation may be required.
3. Drugs:
   - Oral—lamivudine, adefovir, entecavir, telbivudine, tenofovir.
   - Injectable—interferon α, emtricitabine.
4. Current treatment:
   - In HBeAg positive cases, pegylated interferon or tenofovir or entecavir may be used. Interferon is used for 1 year. Oral antiviral drugs are given for a long time.

5. Liver transplantation in HBV—Previously it was thought that liver transplantation is contraindicated in the presence of HBV infection as it recurred in the graft. However, the use of post-liver transplant prophylaxis with lamivudin and hepatitis B immunoglobulin, has reduced the reinfection rate in up to 10% and 5 year survival up to 80%. So, transplantation may be considered.

Q. How to **treat** a patient with incidental finding of positive HBsAg?

A. Incidental HBsAg positive patient should have investigations such as HBeAg, anti-HBe, HBV-DNA and SGPT. Most of this type of patient remain asymptomatic as chronic HBV healthy carrier. In many cases, there is no active liver disease, normal or slightly raised transaminase and the patient is not highly infective, do not develop progressive liver disease although some patients develop reactive hepatitis. There is an annual spontaneous clearance rate of HBsAg of 1 to 2%.

No treatment is necessary. Only regular follow-up and reassurance is needed. Indications of treatment are as above.

Hepatitis D virus (HDV):

- It is called an RNA defective virus, which does not have any independent existence. It requires HBV infection for replication.
- Source and mode of transmission is like HBV.
- Management of HBV effectively cures HDV.

Hepatitis C virus (HCV):

- It is an RNA flavivirus.
- Acute infection is rare. About 80% of the individual exposed to this virus is chronically infected and spontaneous viral clearance is rare. This virus can cause cirrhosis in 20 to 40 years in 20% cases. May lead to hepatoma in cirrhotic patient, risk is 2 to 5% per year.
- Mode of transmission is by transfusion of blood and blood products.
- There are 6 genotypes of this virus (genotype 1 to 6).
- Treatment is by pegylated α interferon given weekly subcutaneously plus oral ribavirin. Genotype 1 needs 12 months treatment.
- Liver transplantation should be considered when complication of cirrhosis occurs such as resistant ascites. However, C infection recurs in the transplanted liver. Up to 15% patient will develop cirrhosis in the grafted liver in 5 years.

Hepatitis E virus (HEV):

- It is an RNA virus.
- Spread via feco-oral route, mostly a self-limiting disease, does not cause chronic liver disease.
- Only serious during pregnancy, may cause acute liver failure which has a high mortality.

Brief Discussion on Weil's Disease (Leptospirosis)

Organism and animal hosts:

- Leptospira icterohaemorrhagiae of rat
- Leptospira pomona of pig
- Leptospira canicola of dog
- Leptospira hardjo of cattle.

Q. What is **Weil's disease?** What is it's mode of infection, clinical features, investigation and treatment?

A. It is a leptospiral disease caused by leptospira icterohaemorrhagiae characterized by high fever, jaundice, hemorrhage and renal impairment.

Mode of infection: Spread is typically by contact with infected rat urine.

Incubation period: 7 to 14 days.

Clinical features: There are 2 phases –

1. Leptospiremic or bacteremic phase: This phase lasts for one week. Organisms may be found in blood and CSF. Characterized by:
   - High fever with chill
   - Anorexia, nausea, vomiting
   - Headache, myalgia (mainly calf and back)
   - Conjunctival suffusion (blood shot eyes)
   - Skin rash (maculopapular, purpura, bruise, etc.)
   - Lymphadenopathy
   - Jaundice, hepatosplenomegaly
   - In severe case, renal impairment (caused by impaired renal perfusion and acute tubular necrosis, manifested as oliguria or anuria) and hemorrhage (epistaxis, hematemesis, melena, etc.) may occur. There may be liver failure, myocarditis, pulmonary hemorrhage, encephalitis, aseptic meningitis may occur. There may be cardiac failure, hemolytic anemia, thrombocytopenia
   - Relative bradycardia, neck rigidity may be found.
2. Immunological phase: There is development of antibody, leptospira disappears from blood. It lasts for 2 to 5 days. Features are usually mild, but meningism or aseptic meningitis and iridocyclitis may occur. Majority recover uneventfully.

Note Remember the following:

Any patient with high fever, jaundice, bleeding manifestations and renal involvement, Weil's disease is a strong possibility.

Investigations:

- CBC—usually polymorphoneuclear leucocytosis, thrombocytopenia in severe case.
- Blood culture (Fletchur's media)—positive in 1st week of illness (within 4 days of illness).
- Urine R/E—proteinuria, hematuria, RBC cast.
- Urine culture for leptospira in second week.
- LFT—high bilirubin, SGPT and prothrombin time.
- Serum CPK—high.
- Serological test—MAT (microscopic agglutination test) positive at the end of 1st week. ELISA, immunofluorescence technique, etc. may be done.
- CSF study—abnormal in 90% cases.
- PCR—leptospira DNA by PCR in blood can be detected in early symptomatic disease and also in urine from 8th day of illness, may remain for months thereafter.

Treatment:

1. Antibiotic:
   - IV benzyl penicillin (1.5 million units 6 hourly for 1 week) or ampicillin (1g 6 hourly for 1 week). Ceftriaxone (1 g daily for 1 week) is as effective as penicillin.

- Doxycycline (100 mg 12 hourly for 1 week) or ampicillin (750 mg 6 hourly for 1 week) when started within 4 days of onset of symptoms.

2. In renal failure and jaundice:
   - Fluid and electrolyte balance must be maintained
   - Dialysis may be needed
   - Exchange transfusion may be needed in severe hyperbilirubinemia.
3. If anemia and thrombocytopenia—blood transfusion may be needed.

Prophylaxis: Doxycycline 200 mg weekly may have a role.

CHRONIC LIVER DISEASE (CIRRHOSIS OF LIVER)

CHIEF COMPLAINTS

- Swelling of abdomen for … months
- Abdominal discomfort and a sense of heaviness for … months
- Scanty micturition for … months
- Weakness, malaise, loss of appetite for … months.

HISTORY

History of present illness: The patient states that he was reasonably well about … months back. Since then, he has been suffering from gradual swelling of his abdomen which has increased progressively over the last few days. It is not associated with abdominal pain, but there is discomfort and sense of heaviness. He also complains of scanty micturition, generalized weakness, malaise and loss of appetite for … months. There is no history of hematemesis, melena or loss of consciousness. The patient does not give any history of fever, shortness of breath or cough, puffiness of the face, joint pain, skin rash, pigmentation etc. His bowel habit and sleep pattern are normal.

History of past illness: He suffered from jaundice … year back that lasted for about … months and then subsided. At that time, he took some herbal medications. There is no history of any injection, infusion, blood transfusion, IV drug abuse or sharing of needles.

Personal history

Family history

Drug and treatment history: Mention according to the statement of the patient.

GENERAL EXAMINATION

- The patient is ill looking and emaciated.
- Hepatic facies characterized by – pinched face, sunken eyes, hollowed temporal fossa, pinched up nose, malar prominence, muddy complexion of the skin, shallow and dry face with icteric conjunctiva (mention, if present).
- Mildly icteric and mildly anemic.
- Generalized pigmentation is present. There are few ecchymoses in upper limbs.
- Pitting pedal edema—present.
- Multiple spider angiomas are present over the upper part of chest and back.
- There is generalized clubbing, leukonychia (fingers and toes) and palmar erythema.
- Gynecomastia present.
- No koilonychia or cyanosis.
- No lymphadenopathy or thyromegaly.
- Dupuytren's contracture and flapping tremor are absent.
- Pulse—88/min.
- BP—110/75 mm Hg.
- Temperature—99°F.
- Respiratory rate—18/min.

SYSTEMIC EXAMINATION

Gastrointestinal System

- Lips, gums, teeth, tongue and oral cavity—normal.

Abdomen

Inspection:

- The abdomen is distended, flanks are full
- Umbilicus—everted
- Visible superficial veins with normal flow (away from umbilicus)
- There is no visible peristalsis, no scar mark.

Palpation:

- Liver—not palpable.
- Spleen is palpable, 4 cm from the left costal margin in anterior axillary line towards the right iliac fossa. The surface is smooth, firm in consistency, nontender.
- Kidneys—not ballotable.
- Testes—both testes are atrophied.
- Fluid thrill—present.

Percussion: Shifting dullness present.
Auscultation: No abnormality detected.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr. …, 45 years old, businessman, normotensive, nondiabetic, nonsmoker, nonalcoholic, hailing from …, presented with gradual swelling of abdomen for … months which has increased progressively over the last few days. It is not associated with abdominal pain, but there is discomfort and sense of heaviness. He also complains of scanty micturition, generalized weakness, malaise and loss of appetite for … months. There is no history of hematemesis, melena or loss of consciousness. The patient does not give any history of fever, shortness of breath or cough, puffiness of the face, joint pain, skin rash, pigmentation, etc. His bowel habit and sleep pattern are normal.

In the past medical history, he suffered from jaundice … year back that lasted for about … months and then subsided. At that time, he took some herbal medications. There is no history of any injection, infusion, blood transfusion, I/V drug abuse or sharing of needles. There is no family history of such illness. He was treated with frusemide, vitamins, antacids, etc.

On examination – general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is cirrhosis of the liver with portal hypertension

Q. Why **portal hypertension?**

A. Because, the patient has:

- Splenomegaly
- Ascites.

Note Other features of portal hypertension are (mention if asked):

- Collateral circulation, esophageal varices, hemorrhoid, venous hum (between xiphisternum and umbilicus, called Cruveilhier Baumgarten syndrome).
- Portosystemic encephalopathy.
- Endoscopy shows esophageal varices.

Q. What are the other **possible causes** of ascites in this case?

A. As follows:

- Intra-abdominal malignancy with peritoneal metastasis
- Lymphoma
- Tuberculous peritonitis
- Chronic constrictive peritonitis
- Nephrotic syndrome.

Q. What **investigations** should be done in this case?

A. As follows:

1. LFT (total protein with A/G ratio, and prothrombin time are the two most important tests for CLD. Others are serum bilirubin, SGPT and alkaline phosphatase).
2. USG of whole abdomen (in cirrhosis, liver may be small, shrunken, coarse and high echogenic texture, splenomegaly, ascites and dilated portal vein).
3. Viral markers for HBV (HBsAg, HBeAg, anti-HBc) and for HCV (anti-HCV).
4. Proctoscopy (to test for hemorrhoid).
5. Endoscopy (to see esophageal varices).
6. CT scan of hepatobiliary system may be performed.
7. Liver biopsy under USG control (confirmatory).
8. If CLD is due to other cause, investigation should be done accordingly, such as:
   - If hemochromatosis is suspected serum iron, TIBC and ferritin.
   - If PBC is suspected anti-mitochondrial antibody and other auto-antibodies.
   - In younger age, if Wilson's disease is suspected—serum copper, ceruloplasmin and urinary copper.
   - If α_1 antitrypsin deficiency—serum α_1 antitrypsin (which is sometimes associated with liver disease and also pulmonary emphysema, particularly in smokers).
9. Test for ascitic fluid (cytology, biochemistry, SAAG).
10. Other routine investigations:
    - CBC, ESR
    - Serum urea and creatinine, electrolytes, blood sugar.

Q. What investigations are done to see the **severity** of liver disease?

A. As follows:

- Serum albumin—if < 28 g/L, outlook is poor.
- Prothrombin time—prolong PT indicates severe liver disease.
- Serum electrolytes—low sodium indicates severe liver disease due to a defect in free water clearance.
- Serum creatinine—high creatinine > 130 µmol/L is a marker of worse prognosis.

RELATED QUESTIONS AND ANSWERS

Q. What is chronic liver disease (**CLD**) and **chronic liver failure?**

A. As follows:

- CLD is defined as liver disease for 6 months or longer.
- Chronic liver failure means functional capacity of liver cannot be maintained, and is characterized by encephalopathy and/or ascites. When chronic liver failure occurs, it is called decompensated liver disease.

Q. What is **cirrhosis** of liver? What are the **types?**

A. Cirrhosis of liver is a chronic diffuse liver disease characterized by destruction of liver cells with fibrosis, distortion of normal liver architecture and nodular regeneration due to proliferation of surviving hepatocytes. Three types of cirrhosis are:

- Micronodular—regenerative nodule is usually small, 1 mm size, involving every lobule, also called Laennec's cirrhosis and is common in alcoholics.
- Macronodular—large nodules, common in post-necrotic cirrhosis, found in HBV.
- Rarely, mixed type (micronodular and macronodular).

Q. What are the **causes** of cirrhosis of liver?

A. As follows:

- Chronic viral hepatitis (B or C or B and D).
- Chronic alcoholism.
- Nonalcoholic fatty liver disease (NAFLD).
- Immunological (autoimmune liver disease and primary sclerosing cholangitis).
- Biliary (PBC, secondary biliary cirrhosis and cystic fibrosis).
- Genetic (hemochromatosis, Wilson's disease and α_1-antitrypsin deficiency).
- Budd-Chiari syndrome.
- Drugs—methotrexate.
- Idiopathic or cryptogenic.

Q. What are the **commonest causes** of cirrhosis of liver?

A. Viral infection (B and C), alcohol, nonalcoholic fatty liver disease. In young patient with cirrhosis, Wilson's disease may be an important cause.

Q. What are the **stigmata** of CLD or cirrhosis?

A. As follows:

1. In hands:
   - Palmar erythema (liver palm)
   - Dupuytren's contracture
   - Leukonychia
   - Clubbing
   - Flapping tremor
   - Others—scratch mark, spider angioma, xanthoma, pigmentation, jaundice and cyanosis.
2. In face:
   - Parotid enlargement (bilateral)
   - Xanthelasma
   - Spider angioma (also in neck, arm, forearm, hand and any part above the nipple line)
   - Pigmentation
   - Hepatic facies

- Jaundice
- Cyanosis.

3. In chest and abdomen:
   - Gynecomastia (also spider angioma)
   - Less hair in chest or body, scanty axillary (also pubic hair)
   - Engorged veins in chest and also abdomen (due to portal hypertension)
   - In abdomen—splenomegaly, ascites, engorged veins and Caput Medusae
   - Testis—small and atrophied.
4. Others:
   - Generalized pigmentation (any CLD can cause pigmentation, but commonly in hemochromatosis and primary biliary cirrhosis)
   - Purpura and ecchymosis.

Note The following findings are common in alcoholic cirrhosis:

- Bilateral parotid enlargement
- Florid spider angioma
- Dupuytren's contracture
- Gynecomastia
- Testicular atrophy with loss of body hair.

Q. What **specific findings** will you see in CLD or cirrhosis of liver in a young patient?

A. As follows:

- The eyes should be examined to see KF ring for Wilson's disease.
- In lung, signs of emphysema may be present in case of α_1-antitrypsin deficiency.

Q. What are the **signs** of portal hypertension?

A. As follows:

- Splenomegaly (single definite sign, mild in adult but marked splenomegaly in childhood and adolescent). Hypersplenism is common (there may be pancytopenia).
- Ascites.
- Collateral circulation, esophageal varices, hemorrhoid, venous hum (between xiphisternum and umbilicus called Cruveilhier Baumgarten syndrome).
- Portosystemic encephalopathy.
- Endoscopy shows esophageal varices.

Note Remember the following points:

- Normal portal pressure is 2 to 5 mm Hg. If it is > 12 mm Hg, then sign and symptoms, also complications may develop.
- Portal vein is formed by fusion of superior mesenteric vein and splenic vein.
- In adults, cirrhosis of liver is the common cause of portal hypertension.
- In children, extrahepatic portal vein obstruction is the common cause.

Q. What are the signs of **decompensated cirrhosis?**

A. As follows:

- Ascites
- Increasing jaundice
- Hepatic encephalopathy
- Portal hypertension with variceal bleeding
- Worsening liver function (prolonged PT and low albumin).

Q. What are the **complications** of cirrhosis of liver?

A. As follows:

- Portal hypertension with rupture of esophageal varices (causing hematemesis and melena).
- Portosystemic encephalopathy (hepatic precoma) and hepatic coma
- Hepatorenal syndrome
- Hepatopulmonary syndrome
- Hepatoma
- Spontaneous bacterial peritonitis (SBP).

Q. What are the **bad prognostic signs** of CLD?

A. As follows:

1. Clinical:
   - Increasing jaundice
   - Ascites
   - Portosystemic encephalopathy.
2. Laboratory:
   - Increasing bilirubin
   - Sodium < 120 mmol/L (not due to diuretic)
   - Falling plasma albumin < 30 g/L
   - Prothrombin time – prolonged.

Note Remember the following:

Child-Pugh score can be used to see prognosis.

Child-Pugh classification of prognosis in cirrhosis

Score	1	2	3
Encephalopathy	None	Mild	Marked
Bilirubin (μmol/L) » PBC or sclerosing cholangitis » Other causes of cirrhosis	 <68 <34	 68 to 170 34 to 50	 >170 >50
Albumin (g/L)	>35	28 to 35	<28
Prothrombin time (seconds prolonged)	<4	4 to 6	>6
Ascites	None	Mild	Marked

Add the individual scores: <7 = Child's A, 7 to 9 = Child's B, >9 = Child's C

Child-Pugh grade	Survival (%)			Hepatic deaths (%)
	1 year	5 years	10 years	
A	82	45	25	43
B	62	20	7	72
C	42	20	0	85

Q. What is spontaneous bacterial peritonitis (SBP)?

A. It means infection of ascitic fluid in a patient with cirrhosis of liver, in the absence of any apparently primary source of infection. SBP may develop in 8% cases (may be as high as 20 to 30%). It is usually by single organism (monomicrobial). Source of infection cannot be determined usually (so it is named as spontaneous). It is suspected in any patient with ascites who clinically deteriorates.

Causes of SBP: The infective organism gain access to the peritoneum by hematogenous route or mesenteric lymphatics. Most organisms are enteric origin, mainly *Escherichia coli, Klebsiella*, *Haemophilus*, *Enterococcus*, other enteric Gram-negative organisms, rarely *Pneumococcus* and *Streptococcus*. Anaerobic bacteria are not usually associated with SBP.

Clinical features: In a patient with cirrhosis and ascites, may present with sudden abdominal pain, rebound tenderness, absent bowel sounds and fever. There may be increasing ascites, not responding to diuretic. Abdominal signs may be mild or absent in one-third patients. In these patients, hepatic encephalopathy and fever are the main features.

Ascitic fluid in SBP shows the following:

- Fluid looks cloudy (exudative is with high protein and low sugar).
- Neutrophil counts of fluid > 250/mm^3.
- Ascitic fluid culture in blood culture bottles gives the highest yield of organisms. C/S may be negative.

Treatment of SBP: Pending the result of culture, if neutrophil in ascitic fluid is high, treatment should be started immediately as follows:

- Broad-spectrum antibiotics – cefotaxime 2 g 8 to 12 hourly for at least 5 days.
- Ceftriaxone plus amoxyclav is an alternative.
- Intravenous albumin may reduce mortality.

Prognosis and prevention of SBP: Mortality is 10 to 15%. SBP is an indication for referral to liver transplantation center. Recurrence is common in 70% case within one year. This can be prevented by norfloxacin 400 mg daily or ciprofloxacin 500 mg once or twice daily or co-trimoxazole (1 double strength tablet, 5 days/week). In any patient with acute variceal bleeding, risk of bacterial peritonitis may be reduced by giving injection ceftriaxone 1 g daily or oral norfloxacin. Also, patient with high risk group in cirrhosis (low albumin, increased PT, low ascitic fluid albumin), norfloxacin may be used to prevent bacterial peritonitis.

Note

Occasionally, there may be secondary bacterial infection other than SBP. To differentiate from SBP, the following features in ascitic fluid may suggest secondary bacterial infection -

- Neutrophil > 10,000 (very high).
- Total protein – very high (> 1 g/dL is against SBP, highly suggestive of secondary bacterial infection).
- Glucose < 50 mg%.
- Ascitic LDH > serum LDH.
- Presence of multiple organisms in culture.

Q. What is hepatorenal syndrome?

A. If a patient with cirrhosis and ascites develops renal failure, it is called hepatorenal syndrome. It occurs in 10% cases and is of two types:

- Type 1 hepatorenal syndrome is characterized by progressive oliguria and rapid rise in serum creatinine. There is no proteinuria, urine sodium excretion is low, < 10 mmol/day and urine/plasma osmolality ratio is > 1.5. Prognosis is poor, without treatment median survival is < 1 month.
- Type 2 hepatorenal syndrome occurs with refractory ascites, characterized by moderate and stable increase of serum creatinine. Prognosis is better.

Mechanism of hepatorenal syndrome: Initially there is vasodilatation possibly due to nitric oxide, leading to hypotension. As a result, there is high plasma renin, aldosterone, norepinephrine and vasopressin, leading to vasoconstriction of the renal vasculature. This causes increased preglomerular vascular resistance. There is reduced GFR and also sodium and water retention.

Other mediators like eicosanoids may also be involved.

Renal failure is functional and tubular function is intact. Hepatorenal syndrome may be precipitated by excess diuretic therapy, NSAIDs, diarrhea or paracentesis and infection especially spontaneous bacterial peritonitis.

Treatment:

- Diuretic should be stopped.
- Hypovolemia should be corrected, preferably with albumin.
- Terlipressin or noradrenaline with intravenous albumin may be used.
- Liver transplantation is the best option.

Q. What is **hepatopulmonary syndrome?**

A. Hepatopulmonary syndrome is defined as hypoxemia occurring in patient with advanced liver disease. PaO_2 is < 9.3 κPa or 70 mm Hg. It is due to intrapulmonary vascular dilatation with no evidence of primary pulmonary disease. Hypoxia is due to intrapulmonary arteriovenous communication.

The patient has features of cirrhosis with clubbing, spider angioma and cyanosis. Most patients have no respiratory symptoms. But with more severe disease, the patient is dyspnoic on standing. There is a characteristic reduction of arterial oxygen saturation on standing.

Transthoracic echo shows intrapulmonary shunting (which is probably due to nitric oxide over production) and arterial gas analysis shows low oxygen saturation. HRCT may be helpful for detecting dilated pulmonary vessels.

Liver transplantation is indicated in hepatopulmonary syndrome. Features improve after liver transplantation.

Q. What is **portopulmonary hypertension?**

A. It is defined as pulmonary hypertension and cirrhosis of the liver with portal hypertension. There is normal pulmonary artery wedge pressure. It occurs in 1 to 2% cases of cirrhosis. It is caused by vasoconstriction and obliteration of the pulmonary arterial system due to circulating vasoconstrictors particularly endothelin 1. This leads to breathlessness and fatigue. It may respond to medical therapy.

Severe pulmonary hypertension is a contraindication for liver transplantation.

Read the following Topics in Relation to CLD

Portosystemic anastomosis (between portal and systemic veins). Sites are:

1. At the lower end of oesophagus—esophageal tributaries of left gastric vein (portal) communicate with esophageal tributaries of hemiazygos veins (systemic).
2. At the lower end of rectum and anal canal—superior rectal vein (portal) communicates with middle and inferior rectal veins (systemic).

3. Anterior abdominal wall (around the umbilicus):
   - Paraumbilical vein (portal) communicates with systemic veins in epigastric, lateral thoracic, intercostal and lumbar veins.
   - Paraumbilical vein (portal) communicates with diaphragmatic veins (systemic) by a number of small veins, called accessory portal system of Sappey.
4. At bare area of liver—portal radicles of liver communicates with diaphragmatic veins (systemic).
5. At retroperitoneal site—the splenic and colic veins (portal) communicate with left renal veins and other tributaries of IVC by small veins, called veins of Retzius.
6. At the fissure for ligamentum venosum, rarely, persistent ductus venosus establishes direct porto-caval anastomosis (in fetal life, left branch of portal vein at the porta hepatis communicates with IVC via ductus venosus. After birth, ductus venosus is fibrosed to form ligamentum venosum).

Spider angioma

It consists of central arteriole from which numerous capillaries radiate, looks like spider legs. Size varies from pinhead to 1 to 2 mm (sometimes 1 to 2 cm). These are found along the area of SVC, commonly in neck, face, chest and dorsum of hand and above the nipple lines, cause of which is not known. It blanches on pressure, may pulsate if large. Better seen with glass slide or pinhead.

Causes of spider angioma:

1. Physiological:
   - Rarely present in normal people (2%), one to two in number, common in children. If > 2 in number, it is usually pathological, especially in male than female.
   - Pregnancy (usually in the third trimester, disappears after 2 months of delivery).
2. Pathological:
   - CLD, commonly in alcoholic cirrhosis (disappears with improvement of liver function, appearance of new spider indicates deterioration of liver function).
   - Viral hepatitis (transient).
   - Estrogen therapy and estrogen-containing oral contraceptive pill.
   - Rarely, in rheumatoid arthritis, thyrotoxicosis.

Mechanism of spider angioma:

- Due to hyperdynamic circulation
- Excess estrogen level (due to reduced metabolism by the liver).

Differential diagnoses of spider angioma:

- Purpura (spontaneous bleeding into skin and mucous membrane, does not blanch on pressure and there is progressive color change)
- Hereditary hemorrhagic telangiectasia
- Campbell de Morgan spots
- Venous stars.

Venous stars

These are 2 to 3 cm lesions that occur on dorsum of foot, leg, back and lower chest. Caused by elevated venous pressure and are usually found overlying the main tributary of large veins. Do not blanch on pressure and blood flow is from periphery to the center of lesion (opposite to spider angioma).

Palmar erythema (liver palm)

Redness in thenar and hypothenar eminence and pulp of fingers. Blanches on pressure. With glass slide, flushes synchronously with pulse. Causes of palmar erythema:

1. Physiological:
   - Normal people, may be familial
   - Pregnancy.
2. Pathological:
   - CLD (commonly alcoholic cirrhosis)
   - Thyrotoxicosis
   - Polycythemia
   - Prolonged rheumatoid arthritis
   - Chronic leukemia
   - Febrile illness.

Mechanism of palmar erythema in CLD:
- Hyperdynamic circulation
- Probably, high estrogen (controversial).

Q. Why **itching** in liver disease?

A. Common in primary biliary cirrhosis and obstructive jaundice. Actual cause is unknown, probably due to upregulation of opioid receptors and increased levels of endogenous opioids.

Q. What are the **vitamin K-dependent** coagulation factors?

A. Factors II, VII, IX and X (which are produced by liver).

Q. In which liver disease, vitamin K therapy is **helpful?**

A. Usually in obstructive jaundice, as bile salt is necessary for absorption of vitamin K. Less or not helpful in parenchymal liver disease, as vitamin K is not used or less used by the diseased liver.

Note Remember the following:

PT depends on factors I, II, V, VII and X. In CLD, the PT is prolonged, when these factors fall below 30%.

Flapping tremor (asterixis)

It is characterized by irregular, flexion-extension movement of wrist and MCP joints, abduction-adduction of fingers, produced by dorsiflexion of wrist and spreading of the fingers. It is called flapping, because of resemblance to a bird flapping its wings. It is demonstrated by asking the patient to stretch out arms in front, separate the fingers, dorsiflexion of wrist with fixed forearm by the examiner's hand.

If it is present, there is:
- Jerky, irregular, flexion-extension of wrist and MCP joint (looks like goodbye).
- Accompanied by lateral movement of fingers or abduction-adduction of fingers.

Features of flapping tremor:
- It is absent at rest, produced by intentional movement, maximum at sustained posture.
- Usually bilateral, and not necessarily synchronous on each side.
- Disappears during coma.
- Occasionally arms, face, neck, tongue, jaw and eyelids are involved.

Causes of flapping tremor:
- Hepatic encephalopathy (the commonest cause)
- Severe cardiac failure
- Respiratory failure

- Renal failure
- Other causes (rare)—cerebrovascular accident (CVA), drug toxicity (phenytoin and barbiturate), acute focal parietal or thalamic lesion (vascular) and hypoglycemia.

Mechanism of flapping tremor in CLD:

- It is due to impaired inflow of joint position sense and other afferent informations to the brainstem reticular formation, resulting in rhythmical lapse of postural muscle tone.

Q. What is **fetor hepaticus?**

A. It is a bad smell (slightly fecal) of breath, like that of dead mouse, due to methylmercaptan, exhaled in breath. It is derived from amino acid methionine, which is not deaminated by the diseased liver. Methylmercaptan is of intestinal origin (reduced by defecation or use of antibiotics). Presence of fetor hepaticus indicates severe hepatocellular failure with collateral circulation.

Q. What are the **causes of bad breath (halitosis)?**

A. As follows:

- Hepatic precoma (called fetor hepaticus, like dead mouse).
- Diabetic ketoacidosis (sweetish due to ketone body).
- Uremia (fishy ammoniacal).
- Lung abscess with anaerobic infection (may be foetid).
- Others—faulty oral hygiene and alcoholism.

Dupuytren's contracture

It is characterized by thickening, fibrosis and shortening of superficial palmar fascia, causing flexion contracture of fingers. The ring and little fingers are commonly affected and also other fingers are affected. Inability to extend the fingers fully is associated with puckering of the skin and presence of palpable nodules. Usually painless, bilateral, age related, 5 times common in male than in female, often familial with dominant inheritance. It may affect the sole of foot also. It is slowly progressive and fasciotomy is seldom necessary.

Causes are:

- Cirrhosis of liver (commonly alcoholic)
- Alcoholism (itself, not by cirrhosis)
- Prolonged antiepileptic drug (phenytoin)
- Manual worker (gardener) and chronic vibration injury
- Traumatic
- Familial (as autosomal dominant, associated with Garrod's patch on dorsum of hand)
- Diabetes mellitus (diabetic cheiroarthropathy, confuses with systemic sclerosis)
- Peyronie's disease
- Idiopathic (in many cases).

Q. What is **diabetic cheiroarthropathy?**

A. It is a complication of long-standing diabetes mellitus, in which skin of the dorsum of fingers is tight, waxy, shiny and depigmented with joint stiffness and flexion deformities of many fingers. Usually painless, limitation of joint movement may be present, sometimes painful. There is inability to extend the MCP or IP (interphalangeal) joint of at least one finger bilaterally. This can be better detected by prayer sign. Occasionally, affects the wrist and shoulders. Cause of cheiroarthropathy is unknown. There is probably cross-linking and thickening of collagen. It occurs in any type of diabetes mellitus. It is confused with systemic sclerosis. There is no specific treatment.

Portosystemic Encephalopathy (PSE) or Hepatic Precoma

Definition: Portosystemic encephalopathy is a state of neuropsychiatric syndrome due to biochemical disturbance of brain function, caused by chronic liver disease. It may progress from confusion to coma. Liver failure and portosystemic shunting are two important factors for PSE. It is reversible, does not cause marked pathological change in brain and may have cerebral edema in advanced stage.

Mechanism of PSE: It is due to the nitrogenous substances of gut origin that enters into the brain. Normally, these substances are metabolized by healthy liver. In diseased liver, these are not metabolized and enters into the brain through portosystemic shunt.

The PSE can occur in portal hypertension with cirrhosis, also after surgery like portocaval or TIPS shunt.

Nitrogenous substances are:

- Ammonia (produced by intestinal bacteria, which breakdown protein).
- Gamma aminobutyric acid (GABA).
- Amino acid, mercaptan, fatty acids and octopamine, which act as false neurotransmitters.

Factors precipitating PSE (by increasing the availability of nitrogenous substance):

- High dietary protein
- Gastrointestinal bleeding
- Constipation
- Drugs (sedative, antidepressants and diuretics)
- Infection including spontaneous bacterial peritonitis
- Fluid and electrolyte imbalance (hypokalemia)
- Trauma
- Surgery (shunt surgery, TIPSS or other surgery)
- Paracentesis (> 3 to 5 L)
- Development of hepatocellular carcinoma.

Clinical features of PSE (remember the mnemonic DPIST-F)

- **D: Disturbance** of consciousness (confusion, disorientation, drowsiness, delirium, stupor and later coma).
- **D: Disorder** of sleep (hypersomnia, inversion of sleep and more sleep in daytime).
- **P: Personality** change (childish behavior, abnormal behavior, apathy, irritability).
- **I: Intellectual** deterioration, from simple mathematical calculation to organic mental function. Earliest is constructional apraxia (see below).
- **S: Speech** disturbance (slow, slurred, monotonous and dysphasia) and sleep inversion (daytime sleeping).
- **T: Tremor** (flapping tremor).
- **F: Fetor** hepaticus (sweet musty odor in breath).

Other features are convulsion, exaggerated reflex, extensor plantar response and clonus. Rarely, chronic hepatic encephalopathy may be associated with cerebellar dysfunction, Parkinsonism, spastic paraplegia and dementia.

Q. What are the **differential diagnoses** of PSE?

A. As follows:

- Intracranial bleeding (subdural, extradural hematoma)
- Drug or alcohol intoxication

- Delirium tremens (alcohol withdrawal)
- Hypoglycemia
- Wernicke's encephalopathy
- Primary psychiatric disorder
- Wilson's disease
- Postictal state.

Q. How to **diagnose** PSE in early stage?

A. By EEG, which shows diffuse slowing in frequency of normal α range (8 to 13 Hz) to δ range (1.5 to 3 Hz). However, diagnosis is mostly clinical.

Q. How to **treat** PSE?

A. As follows:

- Possible precipitating factors should be identified and avoided (drugs, constipation, electrolyte imbalance, bleeding).
- **No** sedative and **no** diuretic. No protein restriction is recommended.
- Nutrition—glucose (300 to 400 g/day) orally. If the patient cannot take by mouth, then IV should be given.
- Lactulose—15 to 30 mL 8 hourly (bowel should move at least twice daily). If the patient is unable to take lactulose by mouth, it can be given per rectally (300 mg lactulose in 700 mL saline or sorbitol as retention enema). Lactitol is an alternative to lactulose.
- Low bowel wash (if no response to lactulose, then enema).
- Gut sterilizer—metronidazole (200 mg 8 hourly) or neomycin 1 to 4 g, 4 to 6 hourly (it is ototoxic, less or not used). Rifaximin 400 mg TDS orally is more preferable (not absorbed).
- Correction of electrolyte imbalance (especially hypokalemia).
- Control of infection by antibiotic.
- It is suggested that eradication of *H. pylori* which is ammonia producing may help (not proved).
- Chronic or refractory hepatic encephalopathy is an indication for liver transplantation.
- Other treatment—Zinc deficiency should be corrected, if present.
- If the patient is agitated – oxazepam (10 to 30 mg) may be given by mouth.
- Other therapy includes flumazenil, a benzodiazepine receptor antagonist (may help in some cases).

Q. What is the **mode of action** of lactulose?

A. Lactulose is a non-absorbable disaccharide, reaches the colon intact and is metabolized by colonic bacteria to lactic acid. It acts in the following way:

- Osmotic laxative.
- Lactic acid reduces pH of colonic contents, inhibits ammonia-producing colonic bacteria and reduces ammonia absorption by converting NH_3 to NH_4, which is not absorbed.
- Promotes incorporation of nitrogen into bacteria.

Q. What is **fulminating hepatic failure?**

A. It is a clinical syndrome of encephalopathy characterized by confusion, stupor and coma, resulting from sudden severe impairment of hepatic function, occurring within 8 weeks of onset in the absence of pre-existing liver disease. It is also called acute liver failure. It may be hyperacute (< 7 days), acute (within 8 to 28 days) or subacute (29 days to 12 weeks), between the onset of jaundice and encephalopathy.

The two **commonest causes** are viral hepatitis (commonly B and E, and rarely A) and paracetamol toxicity. Other causes are acute fatty liver in pregnancy, Wilson's disease, following shock and rarely extensive malignancy of liver.

Clinical features are similar to PSE.
Treatment is also similar to PSE. Liver transplantation may be considered.

Q. What is **constructional apraxia?** How to **test** for it?

A. Constructional apraxia means inability to perform a known act in the absence of any motor or sensory disturbance. It is tested in the following way (patient will be unable to do):

- Ask the patient to draw a star.
- Writing disturbance (unable to write or disturbance of writing).
- Ask the patient to make triangle with three match sticks or ask to lighten the cigarette by match stick.
- Reitan's trail making test (it is the ability to join or connect the numbers serially with a pen in a certain fixed time). It becomes prolonged in PSE.

Brief Discussion about Ascites

Q. What are the **causes** of abdominal distension?

A. Fluid, fat, flatus, feces and fetus (5F).

Q. How to **confirm** ascites clinically?

A. By eliciting shifting dullness, also fluid thrill (which is present in tense ascites).

Q. What is **ascites?** How much **fluid** is required to detect ascites?

A. It is the pathological accumulation of free fluid in peritoneal cavity. Usually, 2 liters fluid is necessary to detect clinically (at least 1 liter is necessary, even in thin person). Pleural effusion may be present in 10% cases with ascites, usually on the right side, mostly small, occasionally massive and unusual on left side.

Note Remember the following:

Normally, little amount of fluid is present in peritoneal cavity. In a female, up to 20 mL may be present, which varies with menstruation.

Q. What are the **causes** of ascites?

A. As follows:

1. Liver diseases: Cirrhosis of liver with portal hypertension, hepatoma with secondary inperitoneum, Budd-Chiari syndrome.
2. Abdominal causes: Intra-abdominal malignancy with peritoneal metastasis (such as carcinoma of kidney, stomach, colon and ovary).
3. Peritoneal causes: Peritonitis (tuberculous or pyogenic) and secondaries in the peritoneum.
4. Cardiovascular: Chronic constrictive pericarditis (early ascites) and CCF (ascites occurs later).
5. HypoproteinemiaL: Nephrotic syndrome, malnutrition and malabsorption.
6. Others:
   - Collagen disease (SLE and polyarteritis nodosa)
   - Lymphoma and leukemia
   - Meig's syndrome (ovarian fibroma, ascites and right-sided pleural effusion)
   - Acute pancreatitis
   - Myxedema
   - Chylous ascites.

Common causes of ascites:

- Cirrhosis of liver with portal hypertension (commonest cause, in 80% cases).
- Intra-abdominal malignancy with peritoneal metastasis (usually ovarian and gastrointestinal tract malignancy).
- Tuberculous peritonitis.

Ascites may be exudative or transudative:

1. Transudative causes (protein < 25 g/L):
   - Cirrhosis of liver with portal hypertension
   - Nephrotic syndrome
   - CCF
   - Meig's syndrome
   - Other causes of hypoproteinemia (malnutrition and malabsorption).
2. Exudative causes (protein > 25 g/L):
   - Peritonitis (TB and pyogenic)
   - Malignancy
   - Collagen disease
   - Myxedema
   - Budd-Chiari syndrome
   - Others are acute pancreatitis and chylous ascites.

Causes of hepatomegaly with ascites:

- Hepatoma with secondary in the peritoneum
- Chronic constrictive pericarditis
- Lymphoma
- Budd-chiari syndrome
- Alcoholic hepatitis
- Secondary in the liver with peritoneal carcinomatosis (disseminated malignancy).

Causes of splenomegaly with ascites:

- Cirrhosis of liver with portal hypertension
- Collagen disease (SLE)
- Lymphoma
- Leukemia
- Disseminated TB.

Causes of hemorrhagic ascites:

- Traumatic
- Malignancy
- Ruptured ectopic pregnancy
- Acute hemorrhagic pancreatitis
- Rupture of spleen
- Any cause of bleeding disorder
- Excess anticoagulant
- Occasionally, tuberculous peritonitis.

Causes of straw colored ascites:

- Tuberculous peritonitis
- Occasionally, cirrhosis of liver.

Causes of cloudy ascites:

- Pyogenic infection
- SBP.

Causes of chylous ascites (milky color, high triglyceride and Sudan staining of ascitic fluid shows fat cells):

- Trauma
- Filariasis
- Tuberculosis
- Malignancy.

Q. If the patient has **cirrhosis** and **ascites**, what does it **indicate?**

A. Decompensated cirrhosis with portal hypertension (a bad prognostic sign).

Q. What is the **character** of ascitic fluid in CLD?

A. Usually clear, may be straw or light green colored and transudative.

Q. What is the **single best investigation** to detect ascites?

A. Ultrasonography.

Q. What **investigations** are done in ascites?

A. As follows (according to suspicion of cause):

1. If CLD is suspected, LFT should be done (see CLD).
2. CBC (high ESR in TB and leuocytosis in pyogenic infection).
3. Chest X-ray (TB, cardiomegaly and chronic constrictive pericarditis).
4. USG of abdomen (to see liver, para-aortic lymph nodes, neoplasm and ovary in female).
5. Ascitic fluid tap for the following tests:
   - Naked eye examination (straw colored, blood-stained, serous and chylous).
   - Gram staining and C/S (in pyogenic infection).
   - Cytology (neutrophil > 250 cells/mm^3 or WBC > 500 cells/mm^3 in SBP, high lymphocyte in tuberculous peritonitis).
   - Biochemistry for protein and sugar shows high protein in exudative and low protein in transudative. Simultaneous serum albumin to see **serum ascitic albumin gradient** (see below).
   - If tuberculous peritonitis is suspected—ascitic fluid for ADA, AFB and mycobacterial C/S, PCR.
   - Exfoliative cytology (to see malignant cells).
6. Other tests (according to suspicion of causes).
   - For tuberculous peritonitis—MT.
   - Urine for proteinuria and serum total protein (nephrotic syndrome).
   - Ascitic fluid amylase in acute pancreatitis (> 1000 is highly suggestive).
7. CT scan or MRI (if any growth or mass suspected).
8. Laparoscopy and biopsy.

Serum Ascites Albumin Gradient (SAAG)

It is the difference of albumin between serum and ascitic fluid (calculated by serum albumin minus ascitic albumin, from samples taken at the same time). This gradient correlates directly with portal pressure. It is the single test to differentiate ascites due to portal hypertension from non-portal hypertension.

- If the gradient is > 1.1 g/dL, it indicates CLD with portal hypertension.
- If < 1, no portal hypertension (ascites is likely to be causes other than portal hypertension). It is 97% accurate.

Note Remember the following:

Ascites protein < 25 g/L and SAAG > 1.1 g/dL is usually suggestive of portal hypertension.

Q. What is the **mechanism of ascites** in cirrhosis of liver?

A. It is mainly due to renal reabsorption of sodium and water. Multiple factors are involved, such as:

1. Splanchnic vasodilatation is the main factor for ascites in cirrhosis of liver. This is mediated by vasodilator (mainly nitric oxide), that are released when the portal hypertension causes shunting of blood into the systemic circulation. Due to splanchnic vasodilatation, systemic arterial pressure falls, which leads to activation of renin-angiotensin mechanism with secondary aldosteronism, increased sympathetic activity, increased atrial natriuretic peptide secretion and altered activity of kallikrein-kinin system. All these produce salt and water retention.
2. Other factors are:
   - Combination of splanchnic vasodilatation and portal hypertension alters intestinal capillary permeability, leading to accumulation of fluid in peritoneal cavity.
   - Portal hypertension also increases local hydrostatic pressure and causes increased hepatic lymph production, which accumulates into the peritoneal cavity.
   - Low albumin causes low plasma osmotic pressure, which causes extravasation of fluid.
   - Failure to metabolize vasopressin by the liver, that causes further retention of fluid.

Q. How to **treat** ascites in cirrhosis of liver?

A. As follows:

1. Bedrest. It improves renal flow (in horizontal position) and increases diuresis.
2. Sodium and water restriction:
   - Sodium 88 mmol/day (no added salt), in severe case 40 mmol/day.
   - Water 0.5 to 1 L/day (fluid restriction is not necessary, unless sodium is <125 mmol/L).
   - Avoid salt containing and salt retaining diets and drugs (NSAIDs, steroid).
3. Monitor weight, abdominal girth and urinary output daily. Weight loss should be 0.5 to 1 kg/day (fluid loss should not be more than 1 liter daily).
4. Measure serum electrolyte and creatinine.
5. Few patients will respond to the above therapy.
6. If no response in 4 days with above therapy – diuretic should be given. Aldosterone antagonist such as spironolactone 100 to 400 mg/day is given. If no response, frusemide 40 mg daily is added. If still no response with spironolactone 400 mg plus frusemide 160 mg daily, it is considered as refractory ascites. Prolong use of spironolactone can cause painful gynecomastia and hyperkalemia. Eplerenone 25 mg once daily may be a suitable alternative (does not cause gynecomastia).
7. If no response or refractory ascites
   - Ensure that patient is not taking any salt or salt containing diet or drugs.
   - If serum protein (mainly albumin) is low, diuretics may not respond. Then IV salt-poor albumin followed by IV frusemide may be given. Occasionally IV dextran may be tried.
8. Paracentesis:
   - It is indicated if there is huge ascites with cardiorespiratory embarrassment or resistant ascites.
   - 3 to 5 L of fluid can be removed. It is safe provided circulation is maintained (no fear of hepatic encephalopathy, thought previously). Paracentesis is followed by IV albumin (6 to 8 g/L of

ascetic fluid removed, usually 100 mL of 20% human albumin solution for every 3 liter of ascitic fluid drained). Another plasma expander, such as dextran (8 g/L of ascitic fluid removed) or hemaccel (125 mL/L of ascitic fluid removed) may be used.

9. Other modes of treatment (in resistant ascites)
   - ♦ LeVeen shunt (peritoneovenous): A catheter is used with one-way valve to communicate between peritoneal cavity and internal jugular vein, which allows ascitic fluid to pass directly into the systemic circulation (rarely done now a days). Its main complications are infection, SVC thrombosis, pulmonary edema, bleeding from esophageal varices and DIC.
   - ♦ TIPSS (transjugular intrahepatic portosystemic stent shunt): A stent is placed between portal vein and hepatic vein in liver to make portosystemic shunt. It is carried out under radiological control via internal jugular vein. TIPSS is mainly used to reduce portal pressure and also variceal bleeding. Also, it is helpful to relieve resistant ascites, but does not prolong life. Following its use, frequency of paracentesis and diuretic dose is reduced. It can be done provided reasonable liver function without encephalopathy and minimal disturbance of renal function (TIPSS is ineffective with intrinsic renal disease). Hepatic encephalopathy may occur following TIPSS. This can be managed by reducing the shunt diameter.
   - ♦ Portosystemic shunt surgery: Portocaval or splenorenal shunt. Rarely done now a days. May cause encephalopathy.
10. Liver transplantation may be considered, if all measures fail.

Q. Will you **prefer** paracentesis or TIPSS in refractory ascites?

A. TIPSS is preferable than repeated paracentesis, as large volume of fluid and protein are lost in paracentesis. Moreover, TIPSS can improve survival also.

Q. If a patient of CLD with ascites complains of fever and abdominal pain, what is the likely **diagnosis?**

A. Spontaneous bacterial peritonitis (other causes of fever in CLD with ascites are secondary infection, hepatoma and excess pyrogen accumulation).

Q. What are the **complications** of ascites in CLD?

A. SBP and hepatorenal syndrome.

Q. If patient with CLD **deteriorates**, what are the possibilities?

A. As follows:
- ❖ Spontaneous bacterial peritonitis.
- ❖ Hepatocellular carcinoma.

LIVER ABSCESS

CHIEF COMPLAINTS

- Fever for … days
- Pain in the right upper abdomen for … days
- Loss of appetite, weight loss and malaise for … days.

HISTORY

History of present illness: According to the statement of the patient, he was reasonably well … days back. Since then, he has been suffering from continued high grade fever, highest recorded temperature is 104ºF. Fever is associated with chill and rigor, subsides only after taking paracetamol. He also complains of pain in the right upper abdomen for … days, which is dull aching in nature, radiates to right shoulder, more marked on lying in right lateral position and gradually increasing in severity. The patient also complains of marked weight loss, loss of appetite and malaise. His bowel and bladder habits are normal. There is no complaint of cough or hemoptysis.

He gives no recent history of cholangitis, appendicitis or abdominal trauma.

History of past illness: Nothing significant.

Family history: Nothing contributory.

Personal history: He is nonsmoker, nonalcoholic but chews betel leaves and nuts. He is a truck driver by occupation.

Drug history: He was treated with some antibiotics (mention the names or if not known, then tell that the patient cannot mention the names) and paracetamol without significant relief.

History of allergy: Nothing significant.

GENERAL EXAMINATION

- Ill looking, toxic and slightly emaciated
- Complexion is muddy
- No anemia, jaundice, cyanosis, edema, clubbing, koilonychia or leukonychia
- No lymphadenopathy or thyromegaly
- Pulse—110/min
- BP—110/75 mm Hg
- Respiratory rate—28/min
- Temperature—103°F.

SYSTEMIC EXAMINATION

Gastrointestinal System

- Lips, gums, teeth, tongue and oral cavity—normal.

Abdomen

Inspection:

- The abdomen is scaphoid in shape.
- Movement with respiration is restricted in the upper part of abdomen in right side.
- There is fullness of the intercostal spaces in right lower chest (also edema in right lower part of the chest with punch tenderness on the same site).

Palpation:

- There is tenderness over the right upper quadrant of the abdomen.
- Liver is palpable, … cm from the right costal margin in the mid-clavicular line, extremely tender, with a smooth surface and a sharp margin, soft in consistency. Upper border of the liver dullness is in the right 5th intercostal space and it is tender on percussion. There is no hepatic bruit.
- Spleen—not palpable.
- Kidneys—not ballotable.

Percussion:

- The percussion note is tympanic, ascites is absent.

Auscultation:

- Bowel sound—normal.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 42 years old, a truck driver, normotensive, nondiabetic, nonsmoker, nonalcoholic, hailing from …, presented with high grade continued fever, highest recorded 104ºF, for … days. Fever is associated with chill and rigor, subsides only after taking paracetamol. He also complains of pain in the right upper abdomen for … days, which is dull aching in nature, radiates to right shoulder, more marked on lying in right lateral position and gradually increasing in severity. The patient also complains of marked weight loss, loss of appetite and malaise. His bowel and bladder habits are normal. There is no complaint of cough or hemoptysis. He gives no recent history of cholangitis, appendicitis or abdominal trauma. He was treated with some antibiotics and paracetamol without significant relief. All the members in his family are in good health.

On examination – general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is liver abscess (probably pyogenic)

Q. What are your **differential diagnoses?**

A. As follows:

- Hepatocellular carcinoma
- Acute viral hepatitis
- Congestive cardiac failure
- Acute cholecystitis
- Acute cholangiohepatitis.

Q. Why not **viral hepatitis?**

A. As there is history of high fever with chill and rigor, enlarged tender liver which is associated with fullness of the intercostal spaces and edema in right lower part of the chest with punch tenderness. Also there is no jaundice and absence of prodromal symptoms of viral hepatitis like anorexia, nausea, vomiting, etc.

Q. Why not **congestive cardiac failure?**

A. In CCF, there should be triad of engorged and pulsatile neck veins, dependent edema and enlarged tender liver.

Q. Mention **one single investigation** for the diagnosis.

A. Ultrasonogram of hepatobiliary system.

Q. What **investigations** do you suggest in liver abscess?

A. As follows:

1. Full blood count (leukocytosis in pyogenic liver abscess).
2. LFT (usually high alkaline phosphatase, bilirubin is high in 25% cases. Aminotransferases are usually normal, may be slightly high).
3. Serum albumin (low), a fetoprotein.
4. Chest X-ray (PA view) shows raised right dome of diaphragm, small right-sided pleural effusion or collapse of right lung.
5. Blood for C/S (in pyogenic, positive in 30% cases. In some series, 50 to 80% cases may be positive).
6. Ultrasonogram of the upper abdomen.
7. CT scan (shows multiple bull's eye appearance) or MRI of the upper abdomen may be done.
8. If needed, USG-guided aspiration of pus for C/S (in pyogenic), and amoebae is rarely found in pus.
9. For amebic liver abscess:
   - Immunofluorescent antibody test (positive in 95%)
   - Indirect hemagglutination test (positive in 95%)
   - Complement fixation test
   - ELISA.

Q. What are the **types** of liver abscess?

A. Two types:

- Pyogenic liver abscess
- Amoebic liver abscess.

Q. What are the **causes of pyogenic** liver abscess? What are the **causal organisms?**

A. As follows:

- Ascending cholangitis in biliary obstruction (common bile duct) by stone, stricture and neoplasm, or spreads from empyema of gallbladder.
- Hematogenous:
  - Portal pyemia (mesenteric infection) from intra-abdominal sepsis, suppurative appendicitis and perforation.
  - Septicemia or bacteremia (along the hepatic artery).
- Direct extension from peripheral abscess.
- Trauma.
- Infection of liver tumor or cyst.

Causal organisms are *Escherichia coli*, *Streptococcus milleri*, *Streptococcus faecalis* or other *Streptococcus* species, *Staphylococcus aureus*, *Proteus vulgaris*, anaerobic organisms or bacteroids (from large bowel). Often the infection is mixed.

Q. How does the patient usually **present?**

A. As follows:

Pyogenic liver abscess:

- Fever, may be high with chill and rigor, malaise, anorexia and weight loss
- Abdominal pain, mainly in right upper abdomen, may radiate to right shoulder
- Pleuritic right lower chest pain (may be small pleural effusion, pleural rub)
- Jaundice is usually mild, may be severe in multiple abscesses causing biliary obstruction
- Sometimes, only pyrexia of unknown origin (PUO) may be present.

Note Remember the following:

Single abscess is common in right lobe, multiple abscesses are due to infection secondary to biliary obstruction. Immunocompromised patients are likely to develop liver abscess. Complications include rupture, secondary infection and septicemia.

Amebic liver abscess (common in right lobe, usually single):

- History of diarrhea or intestinal disease (absent in 50% cases)
- Fever (low grade) and pain
- Toxicity is absent.

Note Remember the following:

Amebic liver abscess is usually large, single and located in right lobe. Multiple abscesses may occur in advanced disease.

Q. What is the **character of pus** in amebic liver abscess?

A. Chocolate or anchovy sauce color.

Q. How to **treat liver abscess?**

A. As follows:

1. Pyogenic liver abscess:
   - Antibiotic (amoxicillin plus gentamicin) **plus** metronidazole. Cefoperazone (1 to 2 g IV 12 hourly) with metronidazole (500 mg every 6 hours) is an alternative. To be continued for 2 to 3 weeks, sometimes up to 6 weeks.
   - If larger (>5 cm) liver abscess or not responding to antibiotic therapy, then USG-guided aspiration should be done.
   - Surgical drainage is rarely needed. Even more rarely hepatic resection may be indicated for chronic persistent abscess or pseudotumor.
   - Treatment of the underlying cause like biliary obstruction.
2. Amoebic liver abscess:
   - Metronidazole 800 mg 8 hourly for 10 days or secnidazole 2 g daily for 5 days or tinidazole or ornidazole 2 g daily for 3 days.
   - Nitazoxanide 500 mg 12 hourly for 3 days.
   - Diloxanide furoate 500 mg 8 hourly for 10 days or paromomycin should be given for intestinal infection. This is given after the treatment of amoebic liver abscess.
   - USG guided aspiration should be done if abscess size is large (>5 cm), no response to medical therapy or threaten to burst.

Note Remember the following points:

- Mixed infections may be found in many cases. Hence, antibiotic plus anti-amoebic drugs may be needed.
- Abscess may rupture into pleural cavity, pericardial sac or peritoneal cavity. In such cases, immediate aspiration or surgical drainage is needed.

Q. What are the **differences** between pyogenic and amebic liver abscess?

A. As follows:

Points	Pyogenic	Amebic
1. Organism	*E. coli* and others	*E. histolytica*
2. History	Cholangitis, septicemia	Amebiasis
3. Symptoms	High fever with chill and rigor	Fever mild to moderate, no chill and rigor
4. Neutrophil leukocytosis	Common	Less
5. Ultrasonography	Multiple lesion	Usually single
6. Aspiration	Frank pus	Chocolate and anchovy sauce
7. Prognosis	More fatal (mortality 16%)	Less fatal (<1%)

PRIMARY BILIARY CIRRHOSIS

CHIEF COMPLAINTS

- Itching of the whole body for … months
- Distension of abdomen for … months
- Yellow coloration of eyes … months
- Scanty micturition for … months
- Weakness, nausea and loss of appetite for … months.

HISTORY

History of present illness: The patient states that she was reasonably well about … months back. Since then, she has been suffering from severe, generalized itching which is present throughout the day and night. It is not related to any food or any allergen. The patient also noticed gradual abdominal distention, which is progressively increasing over the last few days. It is not associated with any abdominal pain, but there is discomfort and sense of heaviness in the abdomen. She also complains of yellowish coloration of her eyes and high colored urine, which is gradually increasing. For the last … months, she has also noticed frequent passage of voluminous, pale colored, foul smelling stool, which is not mixed with blood or mucus. The patient is also experiencing loss of appetite, generalized weakness, nausea and occasional vomiting, gradual darkening of her skin and scanty micturition for … months. There is no history of hematemesis, melena, backache or bodyache or loss of consciousness.

History of past illness: There is no history of any injection, infusion, blood transfusion, IV drug abuse or sharing of needles.

Personal history: Mention according to the statement of the patient.

Family history: Nothing significant.

Menstrual history: She has amenorrhea for the last 3 years.

Drug and treatment history: Mention according to the statement of the patient.

GENERAL EXAMINATION

- Ill looking, emaciated and hyperpigmented.
- Moderately icteric, mildly anemic.
- Xanthelasma is present around both eyes (xanthomatous deposit may also be present in elbow, knee, buttock, hand crease and tendocalcaneus).
- There are multiple scratch marks.
- Spider angiomas are present on both front and back of upper chest.
- Generalized clubbing, leukonychia and palmer erythema are present.
- No koilonychia, cyanosis, lymphadenopathy or thyromegaly.
- Dupuytren's contracture and flapping tremor are absent.
- Pulse—88/min.
- BP—120/65 mm Hg.
- Temperature—97°F.
- Respiratory rate—18/min.

SYSTEMIC EXAMINATION

Gastrointestinal System

- Lips, gums, teeth, tongue and oral cavity—normal, but yellowish.

Abdomen

Inspection:

- The abdomen is distended, flanks are full, skin is hyperpigmented
- Umbilicus is everted
- Superficial veins are visible with normal flow (away from umbilicus).

Palpation:

- Liver is palpable, … cm from right costal margin in the mid-clavicular line, non-tender, soft in consistency, with smooth surface and sharp margin. There is no hepatic bruit.
- Spleen is palpable, … cm from the costal margin in left anterior axillary line, towards the right iliac fossa, surface is smooth, consistency is firm, nontender.
- Kidneys—not ballotable.
- Fluid thrill—present.

Percussion: Shifting dullness is present.

Auscultation: Normal.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mrs. …, 49 years old, housewife, normotensive, nondiabetic, nonsmoker, hailing from …, presented with severe, generalized itching for … months. It is present throughout the day and night and not related to any food or any allergen. The patient also noticed gradual abdominal distention, which is progressively increasing over the last few days. It is not associated with any abdominal pain, but there is discomfort and sense of heaviness in the abdomen. She also complains of yellowish coloration of her eyes and high colored urine, which is gradually increasing. For the last … months, she has also noticed frequent passage of voluminous, pale colored, foul smelling stool, which is not mixed with blood or mucus. The patient is also experiencing loss of appetite, generalized weakness, nausea and occasional vomiting, gradual darkening of her skin and scanty micturition for … months. There is no history of hematemesis, melena, backache or bodyache or loss of consciousness. She does not have any history of injection, infusion, blood transfusion, IV drug abuse or sharing of needles. There is no history of such illness in her family. She is amenorrhoic for the last 3 years. She was treated with frusemide, antacids, vitamins, etc. by local physicians.

On examination – general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is primary biliary cirrhosis with portal hypertension.

Q. What are your **differential diagnoses?**

A. As follows:

- Hemochromatosis
- Cirrhosis of the liver due to HBV or HCV infection.

Q. Why it is **PBC?**

A. Because, in this middle-aged lady, there is history of itching, jaundice, steatorrhea, ascites, pigmentation, xanthelasma, scratch marks and hepatosplenomegaly. All are suggestive of PBC.

Q. **Why not** this is a case of cirrhosis of liver?

A. In cirrhosis, usually there is no itching and liver is usually not enlarged (rather small and shrunken).

Q. **Why not** hemochromatosis?

A. Because it is not common in female, usually there is no itching, steatorrhea, xanthelasma, scratch mark, etc. in hemochromatosis.

Q. What **investigations** are done in PBC?

A. As follows:

- LFT (alkaline phosphatase is very high, may be the only finding. Aminotransferases may be elevated, but not more than 5 times of the upper limit. γ GT is also high. Serum total protein and albumin is reduced. There is marked rise of 5-nucleotidases activity).
- USG (hepatomegaly with cirrhotic change, splenomegaly and ascites).
- Anti-mitochondrial antibody is positive in 95% cases (M2 is specific). Other antibodies such as anti-smooth muscle antibody (35%) and antinuclear antibody (25%) may be present.
- Liver biopsy (There is infiltration of lymphocytes and plasma cells in portal tract, destruction of small bile duct with ductal proliferation, piecemeal necrosis and cirrhosis. Granuloma may be present in 40% cases).
- ERCP or MRCP (to rule out extrahepatic biliary obstruction in doubtful cases).
- Others—serum cholesterol (high) and serum immunoglobulin (IgM) is very high.

RELATED QUESTIONS AND ANSWERS

Q. What is **primary biliary cirrhosis?** What are the **causes?**

A. PBC is a chronic, progressive, cholestatic liver disease characterized by granulomatous destruction of interlobular bile ducts, inflammatory damage with fibrosis spreading from portal tract to liver parenchyma and eventual cirrhosis.

Causes: Actual cause is unknown. It is probably an autoimmune disease occurring in a genetically predisposed person, triggered by environmental factors like infections by retrovirus, bacteria including *E. coli* and mycobacteria. None are proved.

Q. What is **secondary biliary cirrhosis?**

A. When cirrhosis develops due to prolonged obstruction of the large biliary ducts. Causes are stone, strictures and sclerosing cholangitis.

Q. How the patient with PBC usually **presents?**

A. PBC is common in middle-aged (40 to 60 years of age) females. Common presentations are:

- May be asymptomatic. Incidental finding like isolated hepatomegaly on routine examination. High alkaline phosphatase in LFT.
- Pruritus may be the early feature, may precede jaundice by many months or years.
- Jaundice (usually with pruritus).
- Abdominal pain or discomfort.
- Malabsorption (steatorrhea).
- Malaise, weakness, loss of weight, hyperpigmentation.
- Others are hepatic osteodystrophy (characterized by bony pain or fracture due to osteoporosis or osteomalacia from malabsorption).

Q. Why itching in PBC?

A. Actual cause of itching is unknown, but probably it is due to upregulation of opioid receptors and increased level of endogenous opioids. This is why opioid antagonist (naltrexone) is used to control itching in PBC.

Q. What are the diseases associated with PBC?

A. PBC is an autoimmune disease, may be associated with other auto-immune diseases, such as:

- Sjogren syndrome
- Thyroid disease (hypothyroidism should be considered especially with fatigue)
- Systemic sclerosis
- Rheumatoid arthritis
- Renal tubular acidosis
- Dermatomyositis
- Addison's disease
- Membranous glomerulonephritis
- Fibrosing alveolitis.

Note Remember the following:

There is high incidence of celiac disease in PBC. It should be excluded when a patient presents with features of malabsorption.

Q. What is anti-mitochondrial antibody (AMA)?

A. It is an antibody directed against mitochondrial pyruvate dehydrogenase complex (PDC) of mitochondrial enzymes. There are 4 types of antigens (M_2, M_4, M_8 and M_9) of which M_2 is specific for PBC. Five M_2 specific antigens have been further identified, of which E_2 component of the pyruvate dehydrogenase complex is the major M_2 autoantigen.

AMA is present in 95% cases of PBC, detected by ELISA (>1:160). It may be positive in auto-immune hepatitis (20%). It is not related to severity and prognosis.

Q. What is the best indicator for prognosis in PBC?

A. Serum bilirubin (if >100 µmol/L, liver transplantation is indicated).

Q. What are the causes of granuloma in liver?

A. As follows:

- PBC
- Tuberculosis
- Sarcoidosis
- Brucellosis
- Parasitic (strongyloidiasis)
- Schistosomiasis
- Drug (phenylbutazone).

Q. How to treat this patient?

A. As follows:

- Urso-deoxycholic acid 10 to 15 mg/kg. (It improves bile flow, replaces toxic hydrophobic bile acid in the bile acid pool, reduces apoptosis of the biliary epithelium. It also improves LFT, slows down histological progress).

- For pruritus, cholestyramine is given, 4 to 16 g/day orally, usually with orange juice. Main dose (8 g) is given before and after breakfast (as duodenal bile acid secretion is more). Alternatively, rifampicin 300 mg/day or naltrexone (opioid antagonist) 25 mg/day up to 300 mg/day may be given. Naloxone is an alternative. In intractable itching, plasmapheresis or liver support device (molecular absorbent recirculating system—MARS) may be considered. Liver transplantation may be indicated in intractable pruritus.
- Vitamins A, D, K and calcium supplement, alfacalcidol (1 mg/day orally).
- If osteoporosis—Bisphosphonate (such as risedronate may be used).
- Liver transplantation should be considered in liver failure. Five years survival is over 80% but recurrence of PBC after transplantation occurs in one-third of cases at 10 years.

Note Remember the following points:

- Colchicine 0.6 mg orally twice daily and methotrexate 15 mg/weekly may be helpful in improving symptoms in some cases.
- Steroid improves biochemical and histological disease, but aggravates osteoporosis and other side effects and should not be used.
- Azathioprine, penicillamine and cyclosporine have no beneficial role.
- In asymptomatic patient, follow-up should be done.

Q. What are the **indications of liver transplantation** in PBC?

A. As follows:

- Advanced liver disease (increasing jaundice with serum bilirubin >100 μmol/L).
- Intractable pruritus.

Q. How **cholestyramine** works?

A. It is a chelating agent, acts by binding pruritogens in intestine and increase excretion in stool. It is ineffective in complete biliary obstruction.

Q. What is the **prognosis** of PBC?

A. As follows:

- Asymptomatic patients or patients presenting with pruritus—survive for more than 20 years.
- Once symptoms like jaundice develops, average survival is around 5 years (may be 7 to 10 years).

Q. What is the risk of **hepatobiliary malignancy** in PBC?

A. It is increased in PBC. Risk factors for malignancy are older age, male sex, prior blood transfusion and signs of cirrhosis and portal hypertension.

HEPATOMA

CHIEF COMPLAINTS

- Upper abdominal discomfort and feeling of a mass for … days
- Loss of appetite, weakness and weight loss for … days
- Distension of abdomen for … days.

HISTORY

History of present illness: According to the patient's statement, he was reasonably alright … days back. Since then, he is complaining of upper abdominal discomfort and occasional dull pain for … days. The pain is not associated with food intake or there is no radiation. This patient is also experiencing a mass in the upper abdomen which is painless but slowly increasing in size. For the last … days, he is also complaining of marked loss of appetite, marked loss of weight and extreme weakness, gradual distension of abdomen, and scanty micturition. His bowel habit is normal. There is no history of fever, vomiting, cough, etc.

History of past illness: The patient has suffered from jaundice 5 years back.

Personal history: He smokes about 20 sticks per day for 25 years but, not an alcoholic. He was an intravenous drug abuser 15 years ago and used to share needles with others. There is no history of exposure.

Family history: He is married and has 2 sons and a daughter. There is no history of such illness in his family.

Drug and treatment history: For his present illness, he was treated by his local physician by frusemide, vitamins, ranitidine, etc. but no improvement.

GENERAL EXAMINATION

- The patient is ill looking and emaciated
- Mildly icteric and mildly anemic
- Clubbing, leukonychia (fingers and toes) and palmar erythema are present, no edema
- There are few spider angioma over the chest and back
- No koilonychia, cyanosis, lymphadenopathy or thyromegaly
- Dupuytren's contracture and flapping tremor are absent
- Pulse—96/min
- BP—110/55 mm Hg
- Temperature—98°F
- Respiratory rate—18/min.

SYSTEMIC EXAMINATION

Gastrointestinal System

- Lips, gums, teeth, tongue and oral cavity—normal.

Abdomen

Inspection:

- The abdomen is distended, flanks are full
- Umbilicus is everted
- Superficial veins are visible with normal flow (away from umbilicus).

Palpation:

- Liver is palpable, … cm from right costal margin in the mid-clavicular line, non-tender, hard in consistency, surface is nodular and irregular, margin is irregular. There is a hard nodular mass measuring 3 × 3 cm on the right lobe. Hepatic bruit is audible over the mass
- Spleen is not palpable
- Kidneys are not ballotable
- Fluid thrill—absent.

Percussion: Shifting dullness—absent.

Auscultation: Normal.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 55 years, laborer, normotensive, nondiabetic, smoker, nonalcoholic, hailing from …, presented with upper abdominal discomfort and occasional dull pain for … days. The pain is not associated with food intake or there is no radiation. This patient is also experiencing a mass in the upper abdomen which is painless but slowly increasing in size. For the last … days, is also complaining of marked loss of appetite, marked loss of weight, extreme weakness, gradual distension of abdomen and scanty micturition. His bowel habit is normal. There is no history of fever, vomiting, cough, etc.

The patient mentioned that he had suffered from jaundice 5 years back. He smokes about 20 sticks per day for 25 years. He is not an alcoholic. He was an intravenous drug abuser 15 years ago and used to share needles with others. There is no history of exposure. He is married and has 2 sons and a daughter. There is no history of such illness in his family. For his present illness, he was treated by his local physician by frusemide, vitamins, ranitidine, etc. but no improvement.

On examination – general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is hepatocellular carcinoma (hepatoma).

Q. What are your **differential diagnoses?**

A. As follows:

- Secondary deposit in liver
- Hydatid cyst
- Polycystic liver
- Macronodular cirrhosis.

Q. Why is this hepatoma?

A. Because the liver is hard, irregular, nodular, non-tender and there is hepatic bruit.

Q. Why not secondary deposit?

A. In secondary, there may be history of a primary carcinoma. The nodules are multiple and small. There may be umbilication, but no hepatic bruit.

Q. What **investigations** are done to diagnose hepatoma?

A. As follows:

1. USG (shows filling defects in 90% of cases).
2. α-fetoprotein—high (60%), normal (one-third). Levels increase with the size of tumor.
3. Others:
   - CT or MRI.
   - Carcinoembryonic antigen (high in secondaries).
   - Plain X-ray of abdomen to see calcification in liver (sunburst calcification).
4. Liver biopsy under USG control. (This is confirmatory, but avoided in patient eligible for transplantation or surgical resection, because of small risk of tumor seeding along the needle tract).
5. Viral markers (HBV and HCV).

Note Remember the following:

Metabolic abnormalities in hepatoma are polycythemia, hypercalcemia, hypoglycemia and porphyria cutanea tarda.

Q. What are the **screening tests** to detect hepatoma in cirrhosis of liver?

A. USG and α-fetoprotein. Ultrasonography, every 3 to 6 months in high-risk group (in B and C infection, alcoholic cirrhosis and hemochromatosis).

RELATED QUESTIONS AND ANSWERS

Q. How to **differentiate** between primary carcinoma (hepatoma) and secondary carcinoma?

A. As follows:

Primary	Secondary
1. History of hepatitis B and C infection or cirrhosis of liver	History of primary carcinoma (GIT, bronchus, breast, thyroid and kidney). No primary source in 50% cases
2. Nodule usually single, may be more	Usually multiple nodules
3. No umbilication over the nodule	There is umbilication (due to necrosis)
4. Bruit present (due to increased vascularity)	No bruit (because of the necrotic lesion)
5. Rub may be present	Rub is more common
6. Investigations: » α-fetoprotein increased » Alkaline phosphatase slightly increased » Carcinoembryonic antigen is normal	Investigations: » α-fetoprotein usually not high » Alkaline phosphatase very high » Carcinoembryonic antigen is high

Q. How to **suspect** that hepatoma has developed in cirrhosis of liver?

A. In the following way:

- Rapid deterioration of general condition

- Pain in right hypochondrium
- Increasing ascites, not responding to usual therapy
- Enlarging liver with appearance of nodule (hard and irregular)
- Presence of bruit
- Biochemically increase α-fetoprotein.

Q. What are the **causes** of hepatoma?

A. As follows:

- Chronic hepatitis B infections. HCC is four times common in those with HBeAg positive, then those with HBsAg alone. 75 to 90% are associated with cirrhosis of liver.
- Chronic hepatitis C infections. Risk of HCC is higher in HCV than HBV. Almost always associated with cirrhosis.
- Cirrhosis of liver—in alcoholic cirrhosis, nonalcoholic steatohepatitis (NASH), hemochromatosis, Wilson's disease, α_1-antitrypsin deficiency and primary biliary cirrhosis. Macronodular variant is more prone to develop hepatoma.
- Aflatoxin produced by a fungus Aspergillus flavus (from contaminated ground nut grain, stored in tropical condition).
- Chronic arsenicosis.
- Chlonorsis sinensis (a parasitic infection).
- Prolonged androgen therapy, anabolic steroid and oral contraceptive pill (estrogen) may cause hepatoma (usually adenoma, rarely hepatoma).
- Smoking (rare).

Q. What are the other **primary** tumors of liver?

A. Rarely, fibrolamellar hepatocellular carcinoma, common in young adults, affecting equally in male and female, in the absence of hepatitis B and cirrhosis. The tumor is large at presentation, α-fetoprotein is normal. This tumor is treated by surgical resection.

Other primary tumor include hemangioendothelial sarcoma, cholangiocarcinoma, hepatoblastoma, leiomyosarcoma, fibrosarcoma.

Q. What are the **benign tumors** of liver?

A. As follows:

- Hemangioma is the commonest. Rarely, causes symptom. No treatment is required.
- Adenoma, more in females, caused by estrogen containing oral contraceptives, androgen and anabolic steroid. Surgical resection, if pressure symptoms, also if pregnancy is desired (as size is increased in pregnancy).
- Focal nodular hyperplasia.
- Fibroma.
- Leiomyoma.

Q. Why **secondary carcinoma** is more common in the liver?

A. Because, relatively blood flow in liver is more, double blood supply (by portal vein and hepatic artery).

Q. How to **treat** hepatoma?

A. As follows:

- Surgical resection, in non-cirrhotic patient. Recurrence in 50% at 5 years.
- In cirrhotic patient, resection may be done with small tumor and good liver function.
- Liver transplantation (5-year survival is 70% with single tumor < 5 cm, or three tumors < 3 cm). Hepatitis B and C may recur in transplanted liver.

- Percutaneous injection of ethanol, if tumor size is 3 cm or less, 80% cure rate. Recurrence is 50% at 3 years. Repeated injection may be given. It causes tumor necrosis.
- Transcatheter radiofrequency ablation using a single electrode inserted into the tumor under radiological guidance.
- Transcatheter hepatic arterial embolization (transarterial chemoembolization, TACE) by Gelfoam and doxorubicin. TACE is contraindicated in decompensated cirrhosis and multifocal HCC.
- Chemotherapy—doxorubicin may be effective in 30% cases. IV sorafenib, a multikinase inhibitor, is under phase III trial.

Q. What is α-**fetoprotein?** What are the **causes** of high α-fetoprotein?

A. It is a normal component of plasma protein, produced by the fetal liver older than 6 weeks and reaches maximum concentration at 12 to 16 weeks of fetal life. It falls few weeks after birth. Reappearance in blood in adult life is pathognomonic. Causes of high α-fetoprotein:

1. Hepatoma is the commonest, may be very high, > 500 ng/mL in patients with liver disease is highly suggestive. Level increases with size, may be normal in small size.
2. Others:
   - Chronic active hepatitis (indicates hepatocellular regeneration).
   - Acute viral hepatitis (indicates hepatocellular regeneration).
   - Acute hepatic necrosis following paracetamol toxicity.
   - Embryonic tumours of the ovary and testis.
   - Embryonic hepatoblastoma.
   - Rarely, in other malignancy, such as carcinoma of stomach, pancreas, bile duct and gall bladder (usually with large metastasis in liver).
   - During pregnancy (in serum and amniotic fluid), high level indicates neural tube defect (meningomyelocele or anencephaly).

Causes of hepatic bruit:

- Hepatoma is the commonest cause (due to increased vascularity)
- Acute alcoholic hepatitis
- AV fistula in liver (due to trauma or iatrogenic during liver biopsy)
- Hemangioma.

Causes of hepatic rub

- Secondary deposit in the liver
- Trauma
- Infarction in liver
- Perihepatitis in pelvic inflammatory disease (gonococcal or chlamydial in females, called Fitz–Hugh–Curtis syndrome).

Fitz-Hugh-Curtis Syndrome

Fitz-Hugh-Curtis syndrome is caused by *Chlamydia* or *Gonococcus* infection, which tracks up the right paracolic gutter to cause perihepatitis, secondarily from endocervical or urethral infection. It is characterized by fever, pain in the right hypochondrium with radiation to right shoulder, tender hepatomegaly, hepatic rub and small right pleural effusion.

Chlamydia infection is asymptomatic in 80% cases.

Investigation: Endocervical swab for microscopy and special culture, direct fluorescent antibody for *Chlamydia*, ELISA and PCR may be performed.

Treatment: Tetracycline or doxycycline or erythromycin or azithromycin are used for *Chlamydia* infection.

SECONDARIES IN THE LIVER

CHIEF COMPLAINTS

- Loss of appetite, weakness and weight loss for … days
- Pain in upper abdomen for … days.

HISTORY

History of present illness: According to the patient's statement, he was reasonably alright … days back. Since then, he is complaining of gradual loss of appetite and weakness. He has lost about 5 kg body weight in … days. For the last … days, he is suffering from pain in upper abdomen which is dull aching in nature, not related to food intake or bowel movement and without any radiation. He feels occasional nausea, but there is no vomiting. He did not notice any mass in the abdomen. There is no history of fever, cough, chest pain, shortness of breath. His bowel and bladder habits are normal.

History of past illness

Personal history

Family history

Drug and treatment history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient is ill looking and emaciated
- Moderately anemic, but not icteric
- No clubbing, koilonychia, leukonychia, cyanosis or edema
- There is no lymphadenopathy or thyromegaly
- Pulse—108/min
- BP—105/55 mm Hg
- Temperature—97°F
- Respiratory rate—20/min.

SYSTEMIC EXAMINATION

Gastrointestinal System

- Lips, gums, teeth, tongue and oral cavity—normal.

Abdomen

Inspection: Right upper abdomen is distended.

Palpation:

- Liver is palpable … cm from the right costal margin in the midclavicular line, nontender, hard in consistency, surface is nodular and irregular, margin is irregular. Hepatic bruit is absent. Upper margin in the ------ space.
- Spleen is not palpable.
- Kidneys are not ballotable.
- Fluid thrill—absent.

Percussion: Shifting dullness is absent.
Auscultation: Normal.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 65 years, farmer, normotensive, non-diabetic, smoker, non-alcoholic, hailing from …, presented with gradual loss of appetite and weakness for … days. He has lost about 5 kg body weight in … days. For the last … days, he is suffering from pain in upper abdomen which is dull aching in nature, not related to food intake or bowel movement and without any radiation. He feels occasional nausea, but there is no vomiting. He did not notice any mass in the abdomen. There is no history of fever, cough, chest pain, shortness of breath. His bowel and bladder habits are normal. There is no history of such illness in his family. He used to take antacids, vitamins and painkillers.

On examination – general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is secondaries in the liver.

Q. What are your **differential diagnoses?**

A. As follows:
- Hepatoma
- Hydatid cyst
- Polycystic disease of liver.

Q. **Why** is it secondary and not primary?

A. Because there are multiple hard nodules of variable size and shape. There is no bruit. If primary, there is usually a single hard nodule, occasionally with hepatic bruit.

Q. What are the **primary sources?**

A. In male, common primary sources are carcinoma of the stomach, lung and colon. In female, common sources are carcinoma of breast, colon, stomach and uterus. Less common sources for both sexes are carcinoma of the pancreas, gallbladder, carcinoid tumor.

Q. Which tumor is more **common** in liver?

A. Secondaries in the liver is more common (90%), primary hepatic tumor is less common.

Q. How to **diagnose**?

A. As follows:
- Ultrasonogram of the whole abdomen.
- CT or MRI of the abdomen may be done.
- Liver function tests—usually alkaline phosphatase is high.
- Other investigation to find out the primary source according to the history of the patient. For example X-ray chest P/A view, endoscopy of upper GIT, colonoscopy, etc.
- FNAC or USG guided liver biopsy may be done in some cases.

Q. How to **treat** the case?

A. As follows:
- Treatment of the primary cause if possible.
- If solitary metastasis, surgery may be possible (as in colorectal carcinoma).

- If surgery is not possible, radiofrequency ablation of the metastasis may be tried.
- Majority requires palliative treatment.

Q. What is the **prognosis**?

A. Most patients survive less than 6 months. Prognosis is relatively better in colorectal carcinoma with metastasis in the liver.

HEMOCHROMATOSIS

CHIEF COMPLAINTS

- Swelling of abdomen with discomfort for … months
- Swelling of both legs for … months
- Breathlessness on exertion for … months
- Weakness, malaise, loss of appetite for … months
- Generalized pigmentation for … months.

HISTORY

History of present illness: The patient states that he was reasonably well about … months back. Since then, he has noticed gradual swelling of his abdomen, which is increasing progressively over the last few days. It is not associated with any abdominal pain, but the patient feels discomfort and sense of heaviness. He also complains of gradually increasing swelling of his both legs and scanty micturition for the last … months. The patient is experiencing difficulty in breathing after exertion such as walking for some distance or going upstairs for the last … months, and it is progressively becoming worse day by day. There is no history of paroxysmal nocturnal dyspnea or orthopnea. For the last … months, the patient also complains of generalized weakness, malaise, loss of appetite, loss of libido and joint pain involving both the knees. He noticed generalized pigmentation all over his body for … months. He denies any history of cough, puffiness of the face, skin rash, hematemesis, melena, palpitation, chest pain or loss of consciousness, etc. His bowel habit and sleep pattern is normal.

History of past illness: There is no previous history of jaundice or breathlessness.

Personal history: He does not smoke or drink alcohol. There is no history of intravenous drug abuse, sharing of needle or extramarital sexual relationship.

Family history: His father and one uncle also had such illness.

Drug and treatment history: There is no history of any injection, infusion or blood transfusion.

GENERAL EXAMINATION

- Ill looking and emaciated with generalized pigmentation
- Mildly icteric and mildly anemic
- Pitting edema is present
- Multiple spider angiomas are present over the upper part of chest and back
- There is leukonychia (involving fingers and toes) and palmar erythema (in both hands)
- No clubbing, koilonychias or cyanosis
- No lymphadenopathy or thyromegaly
- Dupuytren's contracture and flapping tremor are absent
- Body hair diminished in chest, axillary and pubic region
- Pulse—88/min
- BP—110/75 mm Hg sitting and 95/60 mm standing
- Temperature—99°F
- Respiratory rate—18/min.

SYSTEMIC EXAMINATION

Gastrointestinal System

- Tongue, oral mucosa, hard palate—pigmented.

Abdomen

Inspection:

- The abdomen is distended, flanks are full
- Umbilicus—everted
- Visible superficial veins with normal flow (away from umbilicus)
- There is no visible peristalsis, no scar mark.

Palpation:

- Liver—enlarged, … cm from right costal margin in right midclavicular line, firm in consistency, nontender, with smooth surface and no hepatic bruit.
- Spleen is palpable, 4 cm from the left costal margin in the anterior axillary line towards the right iliac fossa, surface is smooth, firm in consistency, nontender.
- Kidneys—not ballotable.
- Testes—both are atrophied.
- Fluid thrill—present.

Percussion: Shifting dullness is present.
Auscultation: No abnormality detected.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 49 years, businessman, normotensive, nondiabetic, nonsmoker, hailing from …, presented with gradual swelling of abdomen for … months, which is increasing progressively over the last few days. It is not associated with any abdominal pain, but the patient feels discomfort and sense of heaviness. He also complains of gradually increasing swelling of his both legs and scanty micturition for the last … months. The patient is experiencing difficulty in breathing after exertion such as walking for some distance or going upstairs for the last … months, and it is progressively becoming worse day by day. There is no history of paroxysmal nocturnal dyspnea or orthopnea. For the last … months, the patient also complains of generalized weakness, malaise, loss of appetite, loss of libido and joint pain involving both the knees. He noticed generalized pigmentation all over his body for … months. He denies any history of cough, puffiness of the face, skin rash, hematemesis, melena, palpitation, chest pain or loss of consciousness, etc. His bowel habit and sleep pattern is normal. There is no previous history of jaundice or breathlessness. He does not smoke or drink alcohol. There is no history of intravenous drug abuse, sharing of needle or extramarital sexual relationship. There is no history of any injection, infusion or blood transfusion. His father and one uncle also had such illness.

On examination – general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is decompansated cirrhosis of liver with portal hypertension due to hemochromatosis.

Q. What are your differential diagnoses?

A. As follows:

- Decompansated cirrhosis of liver due to HBV or HCV infection or metabolic cause.
- Primary biliary cirrhosis.
- Hepatocellular carcinoma due to cirrhosis of liver.

Q. Why it is hemochromatosis?

A. Because there are features of CLD, generalized pigmentation, arthralgia and testicular atrophy.

Q. Why not PBC?

A. PBC is more common in female and there is long standing generalized itching, xanthelasma, xanthoma, etc.

Q. What is the size of liver in cirrhosis?

A. Small.

Q. What are the cause of hepatomegaly with cirrhosis?

A. Hemochromatosis, primary biliary cirrhosis and alcoholic cirrhosis (early stage).

Q. What investigations should be done in hemochromatosis?

A. As follows:

1. CBC
2. Liver function tests
3. Iron profile:
   - Serum iron (increased)
   - Total iron binding capacity (>70% is saturated)
   - Serum ferritin (increased, > 600 μg/L)
4. CT scan or MRI of hepatobiliary system (increased density of liver due to iron deposits). MRI has high specificity for iron overload, but less sensitivity
5. Hepatic iron index (HII): Shows quantification of liver iron, HII > 1.9 suggests genetic hemochromatosis
6. Liver biopsy (shows iron deposition, hepatic fibrosis, cirrhosis). Liver biopsy to measure the iron stores is a definitive test
7. Others: Blood sugar, ECG, X-ray chest, echocardiogram, X-ray of the involved joint (shows chondrocalcinosis).

RELATED QUESTIONS AND ANSWERS

Q. What are the causes of hemochromatosis?

A. As follows:

1. Primary: Hereditary disorder, inherited as autosomal recessive.
2. Secondary:
   - Hemolytic anemia
     - β thalassemia
     - Sideroblastic anemia
     - Chronic hemolytic anemias.
   - Exogenous iron overload:
     - Repeated blood transfusion (transfusion siderosis)
     - Repeated iron injection
     - Prolonged oral iron.

- Chronic liver diseases:
  - Hepatitis C
  - Porphyria cutanea tarda
  - Alcoholic cirrhosis (in advanced stage).

Q. What is primary hemochromatosis?

A. This is a hereditary disorder, inherited as autosomal recessive, characterized by excess deposition of iron in various organs, leading to fibrosis and functional organ failure. It is associated with HLA-B3, B7 and B14. It is more in male, less in female. However, in female it becomes more in postmenopausal case.

Note Remember the following:

Normal body iron is 3 to 4 grams. In hemochromatosis, it may be 20 to 60 gram. Mainly iron is deposited in liver and pancreatic islets, also in endocrine glands (pituitary, adrenal), heart and skin.

Q. Why hemochromatosis is less in female?

A. Females are protected by iron loss in menstruation and pregnancy.

Q. What is the mechanism (pathogenesis) of primary hemochromatosis?

A. In hemochromatosis, mucosal absorption of iron is more and inappropriate to the body needs. Ultimately progressive accumulation of iron causes elevation of plasma iron, increase saturation of transferrin and high-level of ferritin, which is deposited in different organs of the body.

Q. What are the common features of hemochromatosis?

A. Usually it occurs in male above 40 years. Common features are:

- Liver involvement—hepatomegaly, CLD (about 30% may develop HCC).
- Skin pigmentation (leaden gray skin pigmentation due to melanin deposition).
- Diabetes mellitus.
- Cardiac dysfunction (dilated cardiomyopathy, CCF, arrhythmia).
- Arthritis and chondrocalcinosis.
- Hypogonadism (due to testicular atrophy).

Q. What type of diabetes occurs in hemochromatosis?

A. This is called "bronze diabetes" due to the bronze coloration of the skin.

Q. What are the common causes of pigmentation?

A. As follows:

- Addison's disease
- Hemochromatosis
- Kala-azar
- Arsenicosis
- Drugs—amiodarone, busulfan, bleomycin, phenothiazine, phenytoin, psoralen
- Systemic sclerosis
- Alkaptonuria
- Nelson's syndrome
- Chronic debilitationg illness (malignancy, CLD, CRF).

Q. What are the causes of raised ferritin level?

A. As follows:

- Hemochromatosis
- Alcoholic liver disease

- Hepatitis C infection
- Non-alcoholic steatohepatitis
- As an acute phase reactant in inflammatory and neoplastic conditions
- Adult Still's disease.

Q. How do you **treat** hemochromatosis?

A. As follows:

- Weekly or twice weekly venesection of 500 mL blood (200 to 250 mg of iron is removed) until the serum ferritin is normal. It may take 2 years of more. The aim is to reduce ferritin to <50 µg/L. Thereafter, venesection is continued as required to keep the serum ferritin normal (usually 3 to 4 venesections per year is needed). Following venesection, most of the symptoms improve or disappear, except testicular atrophy, diabetes mellitus and chondrocalcinosis. Joint pain may even worsen.
- Chelation therapy with desferrioxamine (40 to 80 mg/kg/day subcutaneously) may be given. It removes 10 to 20 mg of iron per day. It is mainly used if the patient cannot tolerate venesection, specially those with cardiac disease or severe anemia.
- Symptomatic treatment of cirrhosis, diabetes mellitus (usually by insulin), CCF and cardiac arrhythmia.
- Alcohol must be avoided.
- Supplemental vitamin C must be avoided as pharmacological doses can accelerate iron mobilization to a level that saturates circulating transferrin, resulting in an increase in pro-oxidant and free radical activity.
- First degree family members should be screened.

Note Remember the following:

In primary hemochromatosis, iron is deposited in hepatocytes, whereas in secondary iron overload, iron accumulates in Kupffer cells.

Q. What is the **cause of death** of hemochromatosis?

A. Death is usually due to cardiac failure (30%), hepatocellular failure or portal hypertension (25%) and HCC (30%).

Q. What is the **risk of HCC** in hemochromatosis?

A. HCC usually occurs as a late sequelae in patient who is cirrhotic at presentation. It does not occur if the disease is treated in the pre-cirrhotic stage. In presence of cirrhosis, venesection reduces but does not abolish the risk of HCC.

Q. What is the **prognosis**?

A. If it is diagnosed and treated in pre-cirrhotic stage, life expectancy is normal. Even in cirrhotic patients, there is a good prognosis compaired to other causes of cirrhosis. Three-fourth cases survive 5 years after the diagnosis.

BUDD-CHIARI SYNDROME

CHIEF COMPLAINTS

- Pain and distension of abdomen for … days
- Yellow coloration of the sclera for … days
- Anorexia, nausea and vomiting for … days
- Scanty micturition for … days.

HISTORY

History of present illness: According to the patient, she was reasonably well … days back. Since then, she has been suffering from continuous dull aching pain in upper abdomen which is not associated with food intake. It is more marked on lying on the right side and there is no radiation of pain. She also noticed distension of her abdomen for the same duration, which is gradually increasing, associated with scanty micturition. For last … days, her sclera and urine have turned yellow which is associated with occasional nausea and vomiting. Vomitus contains food material and bile, but no blood. There is no fever, cough, chest pain, hematemesis or melena. Her bowel habit is normal.

History of past illness: There is no past history of jaundice.

Personal history: She is married and has 2 daughters. She is a nonsmoker and nonalcoholic. There is no history of intravenous drug abuse.

Family history: There is no history of similar illness in her family.

Drug and treatment history: She used to take oral contraceptive pills regularly for last 10 years. There is no history of blood transfusion.

GENERAL EXAMINATION

- Ill looking
- Mildly anemic and moderately icteric
- No clubbing, koilonychia, leukonychia, cyanosis or edema
- No lymphadenopathy or thyromegaly
- No stigmata of chronic liver disease
- Pulse—82/min
- BP—110/65 mm Hg
- Temperature—98.6°F
- Respiratory rate—18/min.

SYSTEMIC EXAMINATION

Gastrointestinal System

- Lips, gums, teeth, tongue and oral cavity—normal, but yellowish.

Abdomen

Inspection:

- The abdomen is distended, flanks are full.
- Umbilicus is everted
- Superficial veins are visible with normal flow (away from umbilicus).

Palpation:

- Liver is palpable, … cm from right costal margin in the mid-clavicular line, tender, soft in consistency, with smooth surface and sharp margin. There is no hepatic bruit
- Spleen is not palpable
- Kidneys—not ballotable
- Fluid thrill—present.

Percussion: Shifting dullness is present.
Auscultation: Normal.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mrs …, 40 years, housewife, normotensive, nondiabetic, nonsmoker, hailing from …, presented with continuous dull aching pain in upper abdomen for … days, which is not associated with food intake. It is more marked on lying on the right side and there is no radiation of pain. She also noticed distension of her abdomen for the same duration which is gradually increasing, associated with scanty micturition. For last … days, her sclera and urine have turned yellow which is associated with occasional nausea and vomiting. Vomitus contains food material and bile, but no blood. There is no fever, cough, chest pain, hematemesis or melena. Her bowel habit is normal. There is no past history of jaundice. There is no history of intravenous drug abuse or blood transfusion. She used to take oral contraceptive pills regularly for last 10 years. There is no history of similar illness in her family.

On examination – general examination (mention as above).

Systemic examination (mention as above).

The patient has moderate jaundice, tender hepatomegaly with ascites. The probable diagnoses are:

- Hepatoma with secondaries in the peritoneum
- Secondaries in the liver and peritoneum
- Acute cholangiohepatitis
- Chronic constrictive pericarditis
- Budd-Chiari syndrome.

Q. What are the causes of **enlarged tender liver?**

A. As follows:

- Acute viral hepatitis
- Liver abscess
- Congestive cardiac failure
- Chronic constrictive pericarditis
- Budd-Chiari syndrome

- Hepatoma
- Acute cholangiohepatitis.

Q. What **investigations** are done in Budd-Chiari syndrome?

A. As follows:

1. CBC, ESR, platelet.
2. Liver function tests (serum bilirubin, SGPT, alkaline phosphatase, prothrombin time, serum total protein, A : G ratio).
3. Ultrasonography of whole abdomen, specially doppler ultrasonography (pulsed doppler sonography or a color doppler). It may reveal obliteration of the hepatic veins and reversed flow or associated thrombosis in portal vein.
4. CT or MRI of abdomen:
   - Hepatic vein occlusion with diffuse abnormal parenchyma on contrast-enhancement, which spares the caudate lobe (because of its independent blood supply and venous drainage).
   - There may be compression of the inferior vena cava.
   - Caudate lobe may be enlarged.
5. Venography: Needed if CT and MRI fail to show the hepatic venous anatomy.
6. Aspiration of ascitic fluid: Shows high protein content (above 25 g/L, exudative) in the early stages, but often falls later.
7. Liver biopsy: Shows centrilobular congestion (zone 3), hemorrhage, fibrosis and cirrhosis depending on the duration of illness.
8. Other tests to find out the cause, e.g. coagulation screening (anti-thrombin III, protein S, protein C).

RELATED QUESTIONS AND ANSWERS

Q. What is **Budd-chiari syndrome?**

A. It is a syndrome characterized by obstruction to the venous outflow of the liver due to the occlusion of the hepatic vein and sometimes IVC. This syndrome comprises hepatomegaly, abdominal pain, ascites and hepatic histology showing zone 3 sinusoidal distension and pulling.

Site of obstruction—usually in hepatic vein at any site from the efferent vein of the acinus to the entry of inferior vena cava to right atrium. This type of syndrome may be produced by constrictive pericarditis or right-sided heart failure.

Q. What are the **causes** of Budd-chiari syndrome?

A. The causes are:

1. Hematological disorder that causes thrombosis. It may be due to hypercoagulability states like:
   - Polycythemia rubra vera
   - Paroxysmal nocturnal hemoglobinuria
   - Deficiency of antithrombin III, protein C and protein S
   - Pregnancy and oral contraceptive pill
   - Antiphospholipid syndrome
   - Leukemia.
2. Compression of the hepatic vein due to:
   - Carcinoma of liver, kidney or adrenal gland
   - Posterior abdominal wall sarcoma
   - Hepatic infections (like hydatid cyst)
   - Congenital venous webs
   - Inferior vena caval obstruction.

3. Others: Radiotherapy, trauma to the liver, Behcet's syndrome.
4. Unknown in 1/3rd to half of the cases.

Q. What is the **pathogenesis?**

A. Initially, there is centrilobular venous dilatation and congestion, then centrilobular fibrosis, eventually cirrhosis occurs in those who survive long time.

Q. What are the **usual presentations** of Budd-chiari syndrome?

A. As follows:

- In acute form, there is rapid development of upper abdominal pain, nausea, vomiting, tender hepatomegaly with marked ascites.
- In chronic form or if there is gradual occlusion, there may be gross ascites with upper abdominal discomfort, mild jaundice, splenomegaly.

On examination:

- Hepatomegaly, often tender
- Peripheral edema is present, if there is IVC obstruction
- Those who survive acute events may present with cirrhosis and portal hypertension.

Q. What are your **differential diagnoses** of Budd-chiari syndrome?

A. As follows:

- Inferior vena caval obstruction
- Right-sided cardiac failure
- Chronic constrictive pericarditis CCF.

Q. How to **treat?**

A. As follows:

1. Treatment of predisposing conditions or underlying disorders. For example, if thrombosis is suspected, then treatment with streptokinase followed by heparin and oral anticoagulation should be considered.
2. The following may be considered to relieve obstruction:
   - Short hepatic venous strictures can be treated with angioplasty.
   - More extensive hepatic vein occlusion may be treated with insertion of a covered TIPSS followed by anticoagulation.
   - Side to side portocaval or splenorenal anastomosis may be done if there is no caval obstruction. Surgical shunts are less commonly performed, if TIPSS is available.
   - Congenital webs should be resected surgically.
   - IVC stenosis may be dilated.
3. Ascites is initially treated medically.
4. Liver transplantation is the treatment of choice for chronic Budd-Chiari syndrome and for the fulminant form, followed by life-long anticoagulantion. Progressive liver failure is an indication for liver transplantation and life-long anticoagulation.

Q. What is the **prognosis**?

A. Prognosis depends on the cause. It is poor without liver transplantation or shunting, particularly following an acute presentation with liver failure, but some patients can survive for several years. Following liver transplantation, 1 and 10 years survival is 85% and 69% respectively. This compares with 5- and 10-year survival of 87% and 37% following surgical shunting.

CHAPTER 6

Nephrology

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NEPHROTIC SYNDROME

CHIEF COMPLAINTS

- Swelling of the whole body for … months.
- Scanty micturition for … months.
- Generalized weakness and loss of appetite for … months.

HISTORY

History of present illness: According to the patient's statement, he was alright … months back. Since then, he has been suffering from generalized swelling of the whole body. Initially, he noticed swelling around the eyes and face, followed by arms, abdomen and then legs. He also complains of scanty micturition, but there is no history of burning, hematuria or pain. For the ... months, he is experiencing generalized weakness and loss of appetite. There is no history of sore throat, skin infection, breathlessness, cough, chest pain, bowel abnormality, cold intolerance and jaundice. He did not give any history of skin rash, joint pain or oral ulcers (to exclude collagen disease), or weight loss. There is no history of taking any herbal medicine and nephrotoxic drugs.

History of past illness: Nothing significant.

Family history: Mention according to the patient's statement.

Personal history: He is a student of secondary class, non-smoker.

Socioeconomic history: He comes from a middle class family, lives in a brick built house with good sanitation and water supply.

Drug history: He took frusemide tablets and some antibiotics as prescribed by the local physician.

GENERAL EXAMINATION

- The patient is grossly edematous, the face is puffy with baggy eyelids
- Pitting edema is present
- Mildly anemic
- No clubbing, jaundice, cyanosis, koilonychia, but leukonychia involving all the nails of fingers and toes is present
- No lymphadenopathy or thyromegaly
- Pulse—90/min regular in rhythms
- BP—110/75 mm Hg.

SYSTEMIC EXAMINATION

Gastrointestinal System

Lips, gum, tongue, oral cavity—normal.

Abdomen

1. Inspection:
   - There is generalized distension of abdomen

- Umbilicus is everted
- Scrotum and penis are grossly swollen.

2. Palpation:
   - No organomegaly
   - Kidneys are not ballotable
   - Fluid thrill—present
   - There is no tenderness over the renal angle
   - Genitalia—scrotum and penis are swollen
3. Percussion: Shifting dullness present. There is gross ascites as suggested by presence of shifting dullness and fluid thrill.
4. Auscultation: No abnormality.

Cardiovascular System

There is no abnormality.

Respiratory System

There is no abnormality.

> **Note**
>
> There may be bilateral pleural effusion. If present, mention the signs of pleural effusion.

Examination of the other systems reveals no abnormalities.

Bedside urine for protein +++, sugar nil.

SALIENT FEATURES

Mr. …, 17 years old, student, normotensive, non-diabetic, non-smoker, hailing from …, presented with generalized swelling of the whole body for … months. Initially, he noticed swelling around the eyes and face, followed by arms, abdomen and then legs. He also complains of scanty micturition, but there is no history of burning, hematuria or pain. For the ... months, he is experiencing weakness and loss of appetite. There is no history of sore throat, breathlessness, cough, chest pain, bowel abnormality or cold intolerance and jaundice. He did not give any history of skin rash, joint pain or oral ulcers, or weight loss. For this illness he took frusemide tablets and some antibiotics as prescribed by the local physician. There is no history of taking any herbal medicine and nephrotoxic drugs. There is no family history of such illness.

On Examination—

General examination (mention as above).

Systemic examination (mention as above).

Urine shows gross proteinuria.

My diagnosis is nephrotic syndrome.

(The patient may have bilateral pleural effusion or pericardial effusion. These are often missed while telling the diagnosis).

Q. What are your **differential diagnoses?**

A. As follows:

- Acute glomerulonephritis
- Congestive cardiac failure
- Cirrhosis of the liver
- Hypoproteinemia due to malnutrition or malabsorption.

Q. Why **not** acute glomerulonephritis?

A. Because, in AGN, there will be history of sore throat or skin lesion, no gross or generalized swelling. Also, there may be hypertension and hematuria. Proteinuria is usually mild, urine is smoky.

Q. Why **not** congestive cardiac failure?

A. Because, the signs of CCF are engorged pulsatile neck vein, enlarged tender liver and dependent edema, which are absent in this patient. Usually, there is no generalized edema and no gross proteinuria in CCF.

Q. Why **not** cirrhosis of liver?

A. Because in this patient there are no stigmata or signs of cirrhosis, or CLD. In cirrhosis usually there is only ascites but no generalized edema. Also, in cirrhosis, there is no generalized edema and no gross proteinuria.

Q. What **history** you have taken in NS?

A. As follows:

- Diabetes mellitus
- Malignancy (lymphoma, leukemia)
- Drugs, e.g. captopril, NSAIDs, penicillamine, gold
- Skin rash, arthritis, arthralgia, alopecia (SLE)
- History of other diseases like malaria, leprosy, syphilis, HBV, HCV, amyloidosis, vasculitis
- Family history of sickle cell disease, Alport syndrome, nail patella syndrome.

Q. What **investigations** should be done in nephritic syndrome?

A. As follows:

1. Urine R/E—Shows gross proteinuria. Red cells and red cell casts are absent (also, look for urine sugar to exclude diabetic nephropathy).
2. 24 hours urinary total protein (more than 3.5 g/ 24 h is suggestive of nephritic syndrome).
3. Serum total protein, serum albumin and A:G ratio (hypoalbuminemia).
4. Serum lipid profile (high cholesterol and high TG may be present).
5. Blood sugar, blood urea, serum creatinine, serum electrolytes should be done.
6. USG of the whole abdomen to look for renal pathology.
7. To find out causes:
   - Blood sugar (to exclude diabetic nephropathy).
   - Chest X-ray (to exclude bronchial carcinoma, lymphoma. Also, to see bilateral pleural effusion, pericardial effusion).
   - ANA, Anti-dsDNA (if the history is suggestive of SLE)
   - P-ANCA and c-ANCA (if the history is suggestive of vasculitis)
   - HBsAg and anti HCV screening
   - Complement C3 and C4
   - Renal biopsy (to see the type of GN, whether minimal, membranous or membranoproliferative —this will guide for diagnosis, therapy and prognosis).

RELATED QUESTIONS AND ANSWERS

Q. What is **nephrotic syndrome**? What are the **causes**?

A. Nephrotic syndrome is characterized by generalized edema, massive proteinuria and hypoalbuminemia (with or without hyperlipidemia). Causes are:

1. Primary renal disease—all types of glomerulonephritis (80%):
   - Minimal change glomerular disease (the most common in children)
   - Membranous GN (the most common in adult)
   - Mesangiocapillary and proliferative gomerulonephritis
   - Focal and segmental glomerulosclerosis
   - IgA nephropathy.
2. Secondary to other disease:
   - Diabetic nephropathy
   - Collagen disease, mainly SLE, also rheumatoid arthritis (by amyloidosis)
   - Amyloidosis
   - Drugs—penicillamine (common), captopril, gold, mercury
   - Neoplastic—carcinoma (bronchial carcinoma), lymphoma
   - Infection—malaria (quartan malaria), bacterial endocarditis, HBV, HCV, HIV, secondary syphilis, leprosy
   - Allergies—bee stings, snake bite, anti-snake venom, pollens.

Q. What is the **most common cause** of nephrotic syndrome in children and adult?

A. Most common cause in children is minimal change glomerulonephritis, and the most common cause in adult is membranous glomerulonephritis.

Q. What are the **lipid abnormalities** in NS? What are the **mechanisms**?

A. Lipid abnormalities are:

- Hypercholesterolemia and hypertriglyceridemia
- High LDL, VLDL and IDL
- There is no change or low HDL.

The mechanisms are:

- Increased synthesis of lipoproteins by the liver, secondary to hypoalbuminemia
- Reduced clearance of triglyceride bearing lipoprotein (chylomicron and VLDL) in direct response to albuminuria.

As a result, there is high rate of atherosclerosis.

Q. What is the mechanism of **proteinuria**?

A. There is increased permeability of the glomerular capillary wall due to –

1. Reduction of fixed negatively charged protein molecules in glomerular capillary wall which repel negatively charged protein molecules, allows proteins to pass through the pores
2. Damage to the glomerular basement membrane that leads to increase in the size and number of pores, allowing passage of larger molecules.

Q. Why **edema** in NS?

A. Previously it was thought that reduction of albumin causes low plasma oncotic pressure, which causes to edema. But recent view is oncotic pressure is not changed in NS, edema is due to sodium retention in the extracellular compartment. Also, there is change in molecular barrier, which causes edema.

Q. What is the **blood pressure** in NS?

A. Usually blood pressure is normal, even low. If there is hypertension, usually it is secondary to underlying disease like SLE with renal involvement, polyarteritis nodosa, diabetic nephropathy or terminal stage of nephrotic syndrome.

Q. How to **treat nephrotic syndrome**?

A. As follows:

1. Fluid restriction—depending on previous day's output and patient's edema status (average - 500 mL to 1000 mL/day).
2. Salt restriction.
3. High protein diet (2g/kg/day). In severe case, intravenous salt poor albumin may be given to diuretic resistant patients and those with oliguria and uremia in the absence of severe glomerular damage, e.g. in minimal change nephropathy. It helps in diuresis. Protein intake should be restricted in patient with impaired renal function.
4. Diuretics—loop diuretics (frusemide, bumetanide). If needed, potassium sparing diuretics (spironolactone) should be added.
5. ACE inhibitors and/or angiotensin II receptor antagonists are used in all types of GN (for their antiproteinuric properties. These drugs reduce proteinuria by lowering glomerular capillary filtration pressure).
6. In case of minimal change disease:
   - Prednisolone 60 mg/m^2 body surface area (maximum 80 mg/day) is given for 4 to 6 weeks, followed by 40 mg/m^2 every other day for a further 4 to 6 weeks. More than 95% responds (in children). Alternately, prednisolone 1mg/kg/day up to response (urine protein free) or 3 months followed by tapering the dose in next 3 months.
   - If there is relapse after withdrawal of steroid, it should be given again with gradual withdrawal. Some patients may require low dose maintenance dose (5 to 10 mg/day) for 3 to 6 months.
   - If there is frequent relapse or need high dose steroid or incomplete response to steroid—cyclophosphamide (2.0 mg/kg/day for 8 to 12 weeks) and mycophenolate mofetil with low dose steroid should be given.
7. In membranous glomerulopathy, the following treatment may be given:
   - Inj. methylprednisolone 500 mg to 1000 mg IV for 3 days, followed by oral prednisolone 0.5 mg/kg/day for 27 days in 1st, 3rd and 5th months and Tab. cyclophosphamide 2 mg/kg/day or chlorambucil 0.2 mg/kg/day for 30 days in 2nd, 4th and 6th months.
   - Chlorambucil (0.2 mg/kg/day in months 2, 4 and 6 alternating with oral prednisolone 0.4 mg/kg/day in months 1, 3 and 5) or cyclophosphamide (1.5 to 2.5 mg/kg/day for 6 to 12 months with 1 mg/kg/day of oral prednisolone on alternate days for the first 2 months) are equally effective. However, this treatment is reserved for patients with severe or prolonged nephrosis (proteinuria > 6 gm/day for > 6 months) or renal insufficiency and hypertension.
   - Cyclosporine and mycophenolate mofetil with oral steroid may be used.
   - Anti CD20 antibodies (rituximab) have been shown to improve renal function, reduce proteinuria and increase the serum albumin.
   - Oral high dose corticosteroid and azathioprine are ineffective.
8. Focal and segmental glomerulosclerosis:
   - Symptomatic and supportive treatment.
   - Steroid is effective in 40% cases. Tablet prednisolone 1 mg /kg /day for 3 months then tapered. Total duration of treatment at least about 6 months to 1 year. Most cases progress to renal failure.
   - If no response—MMF 1 to 2 g/day or ciclosporine 5 to 6 mg/kg/ day for 3 months, and maintenances up to 15 months.
   - Tacrolimus 0.05 mg/kg/day may be tried (occasionally effective).
   - Renal transplantation can be done in renal failure, but may relapse after transplantation.

9. Mesangiocapillary or membrano-proliferative GN:
   - Only symptomatic and supportive treatment.
   - No specific treatment.
   - Aspirin may be given.
10. Treatment of complication:
   - If infection—antibiotic is given. Pneumococcal vaccine is recommended.
   - Venous thrombosis—to prevent, prolong bedrest should be avoided. Prophylactic heparin if immobile (enoxaparin may be given), followed by oral anticoagulant.
   - For hyperlipidemia—statin may be added.
11. Treatment of underlying cause, if any.

Q. What is the **prognosis** in NS?

A. It depends on the type of NS.

- Prognosis of minimal change disease in children is excellent. Remission and relapse may occur (common in children and less in adult). CKD does not occur.
- In membranous nephropathy, one-third may remit spontaneously, one-third remain in nephrotic syndrome and one-third shows progressive loss of renal function.
- In FSGS and mesangiocapillary GN—prognosis is bad.
- IgA nephropathy—course of the disease is indolent. ESRD occurs in 20 years.

Q. What are the **complications** of nephrotic syndrome?

A. As follows:

- Hypercoagulability leading to venous thrombosis (especially renal vein thrombosis, also DVT) and pulmonary embolism.
- Infection such as pneumococcal infection (may cause peritonitis and septicemia), cellulitis, streptococcal infection, etc. due to loss of immunoglobulin (IgG deficiency) complements.
- Hyperlipidemia leading to atherosclerosis.
- Oliguric renal failure.
- May cause bilateral pleural effusion, pericardial effusion.
- Loss of thyroxin binding globulin, that causes low FT3 and FT4 which leads to hypothyroidism.
- Loss of transferrin and iron, resulting in iron deficiency anemia.
- Loss of vitamin D binding protein, leading to osteomalacia.

Q. What are the **mechanisms of renal vein thrombosis** in nephrotic syndrome?

A. Mechanisms are as follows:

1. In nephrotic syndrome, there is hypercoagulable state due to:
   - Loss of inhibitors of coagulation in urine, such as antithrombin III, protein C and S, and also loss of fibrinolytic factor (plasminogen).
   - Increase synthesis of clotting factors—factor V, VIII and fibrinogen.
   - Other factors—thrombocytosis and over diuresis resulting in dehydration, reduced renal blood flow and increased viscosity, prolonged bed ridden.
2. Also, there is hyperlipidemia, commonly high LDL, VLDL, cholesterol and triglyceride. So, there is more atherosclerosis.

These predispose to increased venous thrombosis that occurs specially in renal vein.

Note Remember the following:

- In nephrotic syndrome, if there is loin pain, hematuria and deterioration of renal function, it is highly suggestive of renal vein thrombosis. It is more common in membranous nephropaty, mesangiocapillary glomerulonephritis and amyloidosis.
- To diagnose renal vein thrombosis, Doppler ultrasound, CT-Scan or MRI, sometimes renal angiogram (venous phase) may be done.
- Treatment—anticoagulant heparin for 5 to 7 days, then warfarin for 3 to 6 months.

BRIEF DISCUSSION OF DIFFERENT GLOMERULONEPHRITIS

Membranous Glomerulopathy

- It is a common cause of NS in adult, predominantly in males
- It is mostly idiopathic
- May be secondary to—SLE, bronchial carcinoma, drugs (penicillamine), heavy metals like mercury, HBV, HCV
- Renal vein thrombosis is a common complication
- Renal biopsy shows thickening of glomerular basement membrane, increased matrix deposition and glomerulosclerosis
- There is granular subepithelial IgG deposit
- May progress to CKD
- Response to steroid and other cytotoxic drugs is less.

Minimal Change Nephropathy

- Common in children, particularly male, but may occur in all ages, associated with atopy
- On light microscopy, there is no abnormality
- No immune deposit
- On electron microscopy, there is fusion of podocyte foot process
- Progress to renal failure is rare
- Good response to steroid and cytotoxic drugs.

Focal Segmental Glomerulosclerosis

- Segmental scar in glomeruli, no acute inflammation, podocyte foot process fusion may be found. There is C3 and IgM deposition in the affected portions of glomerulus
- Cause is unknown, but may be related to HIV, heroin misuse, morbid obesity, reflux nephropathy, also secondary to any other GN
- Mostly present as idiopathic NS, may progress to renal failure, often resistant to steroid therapy and recurs after renal transplantation
- There is massive proteinuria (usually non selective), hematuria, hypertension and renal impairment.

POST-STREPTOCOCCAL GLOMERULONEPHRITIS (PSGN)

CHIEF COMPLAINTS

- Swelling and puffiness of the face for … day.
- Scanty micturition for … day.
- Generalized weakness, loss of appetite for … day.

HISTORY

History of present illness: According to the patient's statement, she was suffering from pain in the throat with dry cough 3 weeks back from which there was complete recovery. For the last 2 days, she has noticed swelling and puffiness of the face, which is more marked in the morning after waking from sleep. She also complains of scanty micturition, which is slightly smoky and high colored, but no frank blood. The patient also complains of weakness and loss of appetite for the same duration. There is no history of difficulty in breathing, convulsion or unconsciousness or loin pain. She does not give any history of skin infection, arthritis or arthralgia.

History of past illness

Family history

Personal history

Socioeconomic history

Drug history

(Mention according to the patient's statement).

GENERAL EXAMINATION

- Ill looking with puffy face and baggy eyelids
- Mildly anemic
- No edema
- No clubbing, jaundice, cyanosis, leukonychia or koilonychia
- No lymphadenopathy or thyromegaly
- Pulse—110/min
- BP—150/95 mm Hg.

Note Remember the following:

If any skin lesion suggestive of scabies or any skin infection is present, mention it. Diagnosis is then post-streptococcal glomerulonephritis.

SYSTEMIC EXAMINATION

Gastrointestinal System

Mouth, lip, oral cavity—all normal.

Abdomen

1. **Inspection:** No abnormality detected.
2. **Palpation:**
   - No organomegaly
   - Kidneys are not ballotable
   - Fluid thrill—absent
   - There is no tenderness over the renal angle.
3. **Percussion:** Shifting dullness absent.
4. **Auscultation:** No renal bruit.

Cardiovascular System

Heart sounds are normal, no bilateral basal crepitations.

Examination of the other systems reveals no abnormalities.

Examination of urine: Urine is high colored, smoky. There is mild proteinuria.

SALIENT FEATURES

Ms …, 13 years old, student, normotensive, nondiabetic, hailing from …, was suffering from pain in the throat with dry cough 3 weeks back from which there was complete recovery. For the last 2 days, she has noticed swelling and puffiness of the face, which is more marked in the morning after waking from sleep. She also complains of scanty micturition, which is slightly smoky and high colored, but no frank blood. The patient also complains of weakness and loss of appetite for the same duration. There is no history of difficulty in breathing, convulsion or unconsciousness or loin pain. She does not give history of any skin infection, arthritis or arthralgia.

On examination—

General examination (mention as above).
Systemic examination (mention as above).

My diagnosis is acute glomerulonephritis (most likely post-streptococcal).

Q. What is your differential diagnosis?

A. Nephrotic syndrome.

Q. Why not nephrotic syndrome?

A. Because in nephrotic syndrome, there will be generalized edema, massive proteinuria which are absent in this case. (Serum protein will show hypoalbuminemia). In this case, there is acute onset of facial puffiness followed by scanty smoky urine, absence of generalized edema, presence of hypertension. These are against NS.

Q. Why not acute renal failure?

A. Because there is no anorexia, nausea or vomiting. Also, previous history of sore throat followed by scanty micturition is in favor of AGN.

Q. What investigations do you suggest in AGN?

A. As follows:

1. Urine R/E: Urine looks smoky. It shows mild to moderate proteinuria, RBC, RBC cast and granular cast (RBC cast is suggestive of AGN)

2. 24 hours urinary total protein (increases, but less than 3 g/L) and volume is less
3. Blood urea, serum creatinine and serum electrolytes
4. CBC (leukocytosis may be present)
5. ASO titer (may be high in post-streptococcal glomerulonephritis)
6. Throat swab for C/S to find streptococcal infection
7. USG of the whole abdomen (to look for renal pathology)
8. CXR (cardiomegaly or pulmonary edema if LVF)
9. Other investigation according to suspicion of causes:
   - ANA, Anti-dsDNA, C3, C4 (if the history is suggestive of SLE)
   - P-ANCA, C-ANCA (if the history is suggestive of vasculitis)
   - HbsAg, Anti-HCV
   - Renal biopsy may be done in some cases.

Q. What are the different **urinary casts** present in different diseases?

A. As follows:
- RBC cast—AGN
- WBC cast—Pyelonephritis
- Granular cast—GN
- Hyaline cast—Normal finding.

RELATED QUESTIONS AND ANSWERS

Q. What is **AGN**? What are the **causes**?

A. AGN is the inflammation in kidney characterized by hematuria, hypertension, edema (periorbital, leg or sacral) and oliguria. Urine shows proteinuria and red cell cast.

Causes are:
- Infection—post-streptococcal commonest. Other infections include infective endocarditis, infectious mononucleosis, HBV, HCV, etc.
- Non-infectious—SLE, Henoch-Schonlein purpura, cryoglobulinemia, etc.
- Primary glomerular disease—diffuse proliferative GN, IgA nephropathy, membranous GN, focal segmental GN.
- Shunt nephritis.

Q. Why there is **hypertension** in AGN?

A. There is salt and water retention secondary to oliguria. Also, there is secondary hyperaldosteronism.

Q. What are the causes of **glomerulonephritis with low complement?**

A. As follows:
- Post-streptococcal glomerulonephritis
- Lupus nephritis
- Infective endocarditis
- Cryoglobulinemia
- Mesangiocapillary glomerulonephritis (90% in type II and 70% in type I)

Q. What are the **complications** of AGN?

A. As follows:
- Acute renal failure
- Hypertension and its complications, such as acute LVF, CVD, hypertensive encephalopathy
- Fluid and electrolyte imbalance

- Nephrotic syndrome
- May lead to chronic glomerulonephritis.

Q. How to **treat**?

A. As follows:

- Rest
- Fluid restriction (total intake 500 to 1000 mL/day)
- Salt restriction
- Protein restriction, if urea and creatinine are high
- Diuretics (frusemide)—to relief edema. If renal function impairment, dose of diuretics is single and high. But if renal function is normal, then divided and low dose
- If hypertension is present, it should be treated accordingly
- Antibiotic—penicillin (crystalline penicillin or phenoxymethyl penicillin) or erythromycin for 7 to 10 days, especially in post-streptococcal glomerulonephritis.
- Management of complication like pulmonary edema, hypertensive encephalopathy, ARF (dialysis may be required).
- If recovery is slow, corticosteroid may be given.

Post-streptococcal glomerulonephritis (PSGN):

- It is a common cause of acute nephritic illness. Caused by group A beta hemolytic streptococcus of nephritogenic type. But can occur following other infection. Common in children than adult. There is a latent period of about 10 days (1 to 3 weeks) after a throat infection or longer after skin infection (such as infected scabies, impetigo, furunculosis), suggesting an immune mechanism. Even streptococcal otitis media or cellulitis can lead to PSGN.
- It is common with poor personal hygiene, over crowding and skin infection like scabies.
- The patient presents with periorbital edema, hypertension, reduced urinary volume. There is reduction of GFR, proteinuria, hematuria, etc. Urine is red or smoky.
- There is low C_3 and C_4 and evidence of streptococcal infection (high ASO, culture of throat swab).
- Prognosis is usually good in children. A small number of adults develop hypertension and/or renal failure later in life.

Characteristics of AGN in adult:

- Usually no preceding history of infection like sore throat, skin infection, etc.
- Edema is not marked
- Hypertension may or may not be present.

READ THE FOLLOWING TOPICS IN RELATION TO AGN

Causes of puffy face:

- Renal cause—nephrotic syndrome, acute glomerulonephritis
- Myxedema
- Cushing's syndrome
- SVC obstruction
- Angioneurotic edema
- Hypoproteinemia
- Congestive cardiac failure in advanced stage
- Alcoholism
- Acromegaly.

Characteristics of edema in different disease:

- Nephrotic syndrome—edema is generalized. It starts in face, and then involves whole body. May be ascites, bilateral pleural effusion, pericardial effusion, etc. due to hypoalbuminemia.
- Congestive cardiac failure—edema starts in leg (dependent edema). In severe, advanced case, there may be ascites, swelling of face.
- Cirrhosis of liver—first there is ascites, then may be edema in leg.
- Malnutrition or hypoproteinemia—edema of the feet and face, later may be ascites or even generalized.

Causes of red urine:

- Hematuria
- Hemoglobinuria
- Myoglobinuria
- Ingestion of beet root, senna, some dyes used to color sweets
- Drugs—rifampicin, clofazimine, phenindione, purgative like phenolphthaline.

Causes of black urine (fresh urine is normal, but when kept for hours, it turns dark):

- Acute intermittent porphyria
- Alkaptonuria.

Causes of painless hematuria:

- Glomerulonephritis, commonly IgA nephropathy
- Renal tuberculosis
- Tumors of urinary system (renal cell carcinoma, papilloma of the urinary bladder, etc.)
- Bleeding disorder
- Anticoagulant or antiplatelet drug therapy
- Bilharziasis (schistosomiasis)
- Interstitial nephritis.

Cause of painful hematuria:

- Renal infection
- Renal calculi
- Trauma
- Polycystic kidney disease (clot colic)
- Loin pain hematuria syndrome
- Hemorrhagic cystitis due to cyclophosphamide.

Few common definitions:

- **Anuria—**it is defined as failure to pass urine more than 50 mL in 24 hours
- **Oliguria—**failure to pass less than 400 mL of urine in 24 hours
- **Nocturia—**need to get up during the night to pass urine
- **Polyuria—**passing of large volume of urine more than 3 L in 24 hours
- **Frequency of micturition—**repeated scanty urination.

POLYCYSTIC KIDNEY DISEASE

CHIEF COMPLAINTS

- Heaviness and mass in abdomen for … months
- Frequency of micturition for … months
- Occasional pain in both loins for … months.

HISTORY

History present illness: The patient states that she was alright … months back. Since then, she has been experiencing heaviness in the abdomen. It is persistent, not related to any food. Also she feels mass on both sides of the abdomen for the same duration. It is associated with pain in both loins, which is dull aching in nature and does not radiate to any site. The patient also complains of frequency of micturition for … months. It is more marked at night, associated with profuse amount of urine, but no burning or pain. There is no history of hematuria, headache, visual disturbance, unconsciousness, nausea, vomiting or anorexia.

History of past illness: The patient is hypertensive for the last … months. She had recurrent UTI few months back.

Family history: Her mother and one brother also have kidney disease, but does not know the specific type of disease.

Personal history: Mention according to the patient's statement.
Socioeconomic history: Mention according to the patient's statement.
Drug history: She took some antibiotics for her recurrent UTI and is taking atenolol for her hypertension.

GENERAL EXAMINATION

- The patient looks healthy
- No edema, clubbing, jaundice, cyanosis, leukonychia or koilonychia
- No lymphadenopathy or thyromegaly
- Pulse—80/min
- BP—130/85 mm Hg with drug.

SYSTEMIC EXAMINATION

Gastrointestinal System

Lips, gums, teeth, tongue and oral cavity—normal.

Abdomen

1. **Inspection:** Abdomen appears distended, flanks are full.
2. **Palpation:**
   - The kidneys are enlarged and ballotable. The right one is slightly larger than the left which are non-tender and firm with irregular surface, moves with respiration above downward and get above the swelling is possible.

- Fluid thrill—absent.
- Both the renal angles are slightly tender.

3. **Percussion:**
   - Shifting dullness—absent
   - Colonic resonance over the mass is present.
4. **Auscultation—**no renal bruit.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mrs …, 45 years old, housewife, hypertensive, non-diabetic, hailing from …, presented with heaviness in the abdomen for … months. It is persistent, not related to any food. Also she feels mass on both sides of the abdomen for the same duration. It is associated with pain in both loins, which is dull aching in nature and does not radiate to any site. The patient also complains of frequency of micturition for … months. It is more marked at night, associated with profuse amount of urine, but no burning or pain. There is no history of hematuria, headache, visual disturbance, unconsciousness, nausea, vomiting or anorexia. She had recurrent UTI few months back. Her mother and brother also have some kidney disease. She took some antibiotics for her recurrent UTI and is on atenolol for her hypertension.

On Examination—
General examination (mention as above).
Systemic examination (mention as above).

My diagnosis is hypertension with bilateral renal mass, which may be due to polycystic kidney disease.

Q. What is your **differential diagnosis?**

A. Bilateral hydronephrosis with hypertension.

Q. Mention **one** single investigation for your diagnosis.

A. Ultra sonogram of whole abdomen.

Q. What **investigations** should be done in PKD?

A. As follows:

- Ultrasonography (always mention as the first investigation)
- Urine for R/E and C/S
- Full blood count (polycythemia may be found)
- Renal functions—urea, creatinine, serum electrolytes (some patients may be salt looser)
- High resolution CT-Scan or MRI of KUB
- IVU or retrograde pyelography
- Family screening.

Q. What are the **USG criteria** for diagnosis of PKD?

A. USG criteria are:

- Person below 30 years—presence of at least 2 renal cysts (unilateral/bilateral)
- Person between 30 to 59 years—presence of at least 2 renal cysts in each kidney
- Persons 60 years and above—at least 4 cyst in each kidney.

Q. What are the **findings in IVU** in polycystic kidney disease?

A. IVU shows:

- Enlargement of both the kidneys
- Stretching, distortion and elongation of pelvicalyceal system (giving rise to spidery appearance).

RELATED QUESTIONS AND ANSWERS

Q. What is **polycystic kidney disease (PKD)?**

A. It is an inherited cystic disease of the kidney. There are two types:

- Adult PKD (APKD): It is inherited as autosomal dominant, common type, males and females are equally affected. Gene on chromosome 16 (PKD1) and 4 (PKD2).
- Infantile PKD (IPKD): It is inherited as autosomal recessive, rare, associated with cyst in other organs and hepatic fibrosis and fatal in first year due to hepatic or renal failure. Gene on chromosome 6.

Q. What are the **presentations** of adult PKD?

A. As follows:

- May be asymptomatic (renal mass detected on routine examination)
- Discomfort, pain or heaviness in the loin
- Recurrent painful hematuria (due to rupture of cyst in renal pelvis or infection)
- Recurrent UTI
- Acute loin pain or renal colic
- Features of hypertension (usually after 20 years of age) and its complications
- Features of renal failure
- CVA (usually subarachnoid hemorrhage, due to rupture of berry aneurysm. Sometimes, may be cerebral hemorrhage as a complication of hypertension).

Q. What are the **other features** of PKD?

A. As follows:

- Cystic liver—30%, but hepatic dysfunction is rare. There may be cyst in spleen, ovary and pancreas
- Berry aneurysm in circle of Willis—10% (may rupture causing subarachnoid hemorrhage)
- Polycythemia (due to increased erythropoietin secretion)
- Renal stone—10% cases (usually calcium oxalate, urate)
- Renal neoplasm—rarely.

Q. What are the **causes of acute pain** in PKD?

A. Pain is due to:

- Acute hemorrhage in the cyst
- Infection in the cyst
- Renal stone
- Renal cell carcinoma rarely.

Q. If the patient with polycystic kidney disease is **unconscious**, what is likely diagnosis?

A. Subarachnoid hemorrhage due to rupture of berry aneurysm.

Other causes may be:

- Cerebral hemorrhage as a complication of hypertension
- Hyponatremia (salt losing nephropathy).

Q. What are the **causes of death** in PKD?

A. Death may be due to:

- Chronic renal failure (in one third cases)
- Intracerebral hemorrhage (SAH)
- Myocardial infarction.

Q. How to **manage** the patient of PKD?

A. As follows:

- Control of hypertension
- Control of urinary tract infection
- Plenty of fluid
- Salt (there may be salt looser in some cases)
- For renal pain or if large cyst, ultrasonic guided aspiration or laparoscopic cystectomy may be done
- Treatment of renal failure. Dialysis and even renal transplantation may be done
- Genetic counseling
- Family screening—USG of the abdomen should be done in all members of the family over 20 years of age to detect cysts.
- MR angiography to detect berry aneurysm may be considered in some cases, where other members having history of subarachnoid hemorrhage.

Note Remember the following points:

- Polycystic kidney disease is always bilateral (may be unilateral, if other kidney is absent)
- Polycystic kidney disease is a misnomer, cyst occurs in many other organs (liver, spleen)
- More common in sickle cell disease, cystic fibrosis, Huntington's disease
- May be associated with mitral valve prolapse (25%), causing mitral regurgitation, and aortic regurgitation (rarely severe)
- Colonic diverticula may occur
- Abdominal wall hernia
- Polycystic kidney disease is not premalignant
- Hypertension is present in 75% cases
- Usually there is polycythemia due to high erythropoietin level.There may be anemia if there is chronic renal failure (however, hemoglobin level is higher than expected for the degree of renal failure).

Q. What are the causes of **unilateral renal mass?**

A. As follows:

- Renal cell carcinoma
- Hydronephrosis or pyonephrosis
- Renal abscess
- Solitary kidney (due to hypertrophy) in lean and thin person.

Q. What are the causes of **bilateral** renal mass**?**

A. As follows:

- Polycystic kidney disease
- Bilateral hydronephrosis
- Amyloidosis
- Diabetic nephropathy in early stage
- Bilateral renal cell carcinoma (rare)
- Lymphoma (rare).

Q. What are the **cystic diseases** of kidney?

A. As follows:

- Simple cyst, usually congenital
- Acquired cyst, after dialysis (in chronic renal failure)
- Polycystic kidney disease
- **Medullary sponge kidney:** Cause is unknown, but not genetic. Cyst is confined to the papillary collecting ducts. Age 40 to 60 years, prognosis is good. Usually no hypertension or no renal failure.
- **Medullary cystic disease:** Small cysts in cortical area or corticomedullary junction. Renal failure is common, hypertension may occur. The patients usually have polyuria and increased thirst and are salt loser.

READ THE FOLLOWING TOPICS

Types of hematuria:

- **Initial Hematuria:** Presence of blood at the beginning of micturition. It is usually due to penile urethral cause.
- **Terminal hematuria:** Presence of blood at the end of micturition. It is usually due to bladder neck or prostatic urethral cause.
- **Total hematuria:** Presence of blood throughout micturition. It is usually due to bladder or urinary tract disease (such as renal cell carcinoma, papilloma of urinary bladder, UTI, renal stone) or blood dyscrasia or excess anticoagulant.

Urinary incontinence: It means when urine leaks involuntarily. It is of 4 types:

- **Stress incontinence:** Leakage of urine with activity such as coughing, sneezing, lifting any object, exercise. Found in women after child birth and in man after prostate operation.
- **Urge incontinence:** Uncontrolled leakage of urine preceded by strong urge to void urine. It is due to UTI, enlargement of prostate, stone in urinary bladder.
- **Overflow incontinence:** This occurs when the bladder is chronically over distended. Found in benign prostatic enlargement, pelvic surgery leading to pelvic nerve damage.
- **Continual incontinence:** Patient voids urine at any time, at any position due to loss of sphincter efficacy. Found in vesico-vaginal fistula, uretero-vaginal fistula.

Causes of red/dark urine:

- Hematuria (red)
- Hemoglobinuria (dark)
- Myoglobinuria (in rhabdomyolysis)
- Food dye (beet root)
- Drugs—rifampicin (orange), L-dopa (dark on standing), phenophthalein (pink), senna (orange)
- Acute intermittent porphyria (urine becomes dark on standing)
- Alkaptonuria (urine becomes black on standing).

Q. How to **differentiate** between hematuria and hemoglobinuria?

A. As follows:

Points	Hematuria	Hemoglobinuria
1. Urine	Red	Dark
2. Microscopy	RBC present	RBC absent

CHRONIC KIDNEY DISEASE (CKD, DIABETIC NEPHROPATHY)

CHIEF COMPLAINTS

- Weakness and loss of appetite for … months
- Nausea and occasional vomiting for … months
- Scanty micturition for … days
- Swelling and puffiness of the face for … days.

HISTORY

History of present illness: According to the patient's statement, she was alright … years back. At that time, she was diagnosed as diabetes mellitus incidentally. It was treated with insulin for few months, then oral hypoglycemic drugs. About 5 years back, the patient noticed swelling of both lower limbs. After evaluation, it was treated with frusemide. For the last 3 years, she has been suffering from weakness, loss of appetite, nausea and occasional vomiting. Weakness is progressively increasing. Vomitus contains food material but no blood or bile. The patient also noticed swelling of the face and legs which is associated with scanty micturition during daytime and frequently at night, which disturbs her sleep. For the last … months, she noticed gradual swelling of whole body and puffiness of the face, which is more marked after getting up from sleep in the morning. There is marked weight loss over the last … months. Occasionally, she experiences palpitation and breathlessness on exertion. For these complaints, she consulted with a nephrologist who advied immediate hospitalization for further management. Her bowel habit is normal. There is no history of fever, abdominal pain, loin pain, itching, joint pain, skin rash or hematuria.

History of past illness: She is nonhypertensive. She gives history of recurrent UTI for the last ... months. For this, she was treated with several antibiotics by local physicians.

Family history: There is no history of such illness in her family.
Personal history: Mention according to the patient's statement.
Socioeconomic history: Mention according to the patient's statement.
Drug history: She did not take any drug that may be responsible for such illness.

GENERAL EXAMINATION

- The patient is ill looking and pale, with puffy face and baggy eyelids
- Moderately anemic
- Pitting edema—present
- There is leukonychia (or half and half nail—proximal brown, distal whitish) involving all the fingers and toes
- No clubbing, jaundice, cyanosis or koilonychia
- No lymphadenopathy or thyromegaly
- Skin—multiple scratch marks are present, also there is pigmentation
- Pulse—110/min
- BP—160/95 mm Hg.

(If any fistula for dialysis, comment on it).

SYSTEMIC EXAMINATION

Gastrointestinal System

Lip, teeth, oral cavity, tongue—normal but tongue is pale.

Abdomen

- **Inspection:** No abnormality detected
- **Palpation:**
  - No organomegaly
  - Kidneys are not ballotable
  - Fluid thrill—absent
  - There is no tenderness over the renal angle
- **Percussion:** Shifting dullness absent
- **Auscultation:** No renal bruit.

Nervous System:

- **Higher psychic functions**—normal
- **Cranial nerves**—normal
- **Motor function**—normal
- **Sensory function**—normal
- **Fundoscopy**—diabetic retinopathy grade II.

(However, in motor function, there may be muscular weakness, diminished reflexes, planter equivocal. All are related to neuropathy. Also, in sensory function—there may be reduction of pain, touch, temperature in the legs and hands, due to peripheral neuropathy. So, mention according to your findings.)

Bedside urine examination: Sugar present, protein +++.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mrs. …, 60 years old, housewife, normotensive, nonsmoker, hailing from …, was diagnosed as diabetes mellitus … years back. It was treated with insulin for few months, then oral hypoglycemic drugs. About 5 years back, the patient noticed swelling of both lower limbs. After evaluation, it was treated with frusemide. For the last 3 years, she has been suffering from weakness, loss of appetite, nausea and occasional vomiting. Weakness is progressively increasing. Vomitus contains food material but no blood or bile. The patient also noticed swelling of the face and legs, which is associated with scanty micturition during daytime and frequently at night, which disturbs her sleep. For the last … months, she noticed gradual swelling of whole body and puffiness of the face, which is more marked after getting up from sleep in the morning. There is marked weight loss over the last … months. Occasionally, she experiences palpitation and breathlessness on exertion. For these complaints, she consulted with a nephrologist who advised immediate hospitalization for further management. Her bowel habit is normal. There is no history of fever, abdominal pain, loin pain, itching, joint pain, skin rash or hematuria.

She gives history of recurrent UTI for the last ... months, for which she was treated with several antibiotics by local physicians. There is no history of such illness in her family. She did not take any drug that may be responsible for such illness.

On Examination—
General examination (mention as above).
Systemic examination (mention as above).

My diagnosis is chronic kidney disease (CKD) due to diabetic nephropathy.

Q. What investigations do you suggest in CKD?

A. As follows:

- Urine R/E (to see pus cell, RBC or WBC cast, glycosuria, proteinuria, etc.)
- CBC with PBF (shows normocytic, normochromic anemia)
- Renal function tests (blood urea and serum creatinine are elevated)
- Creatinine clearance
- Serum electrolytes
- Serum calcium (low) and phosphate (high)
- Serum uric acid (may be high)
- Plain X-ray abdomen (calcification, renal stone, kidney size may be seen)
- USG of the whole abdomen (shows shrunken kidneys. Kidneys may be large in diabetic glomerulosclerosis, amyloidosis, PKD and bilateral hydronephrosis)
- CT scan of abdomen
- IVU (rarely needed)
- Isotope renogram
- Renal biopsy (may be needed in some cases)
- Other investigation according to suspicion of cause (ANA and anti ds-DNA for SLE, screening for hepatitis B and C, HIV, etc.).

RELATED QUESTIONS AND ANSWERS

Q. What is **CKD** and what is **ESRD**?

A. As follows:

- CKD is the irreversible deterioration of renal function, classically developing over a period of years
- End stage renal disease or failure (ESRD) is a stage when renal replacement therapy is compulsory either dialysis or renal transplantation, without which death is likely.

Q. What is **acute renal failure?** What are the **causes?**

A. Sudden deterioration in renal function, occurring within weeks or months (<3 months), biochemically detected by high urea and creatinine level. This is usually reversible.

Causes of ARF:

1. Prerenal:
   - Fluid loss due to diarrhea, vomiting, dehydration, etc
   - Blood loss due to hemorrhage.
   - Plasma loss in burn
   - Hypotension due to myocardial infarction, shock, vasodilator drugs, heart failure
   - Rhabdomyolysis
   - Hemolytic uremic syndrome
   - Hepatorenal syndrome
   - Renal artery occlusion or stenosis
   - Disease affecting arterioles.

(Under perfusion to the kidney initially causes rapidly reversible changes. Subsequently, acute tubular necrosis or other changes cause long lasting but usually temporary intrinsic renal failure.)

2. Renal (intrinsic renal disease):
   - Acute tubular necrosis or toxic or septic renal failure (85%)
   - RPGN, due to:
     a. Primary GN, e.g. MCGN, IgA nephropathy
     b. Systemic disease such as SLE, rheumatoid arthritis, systemic sclerosis, multiple myeloma, vasculitis
   - Tubulo-interstitial disease (10%) due to drugs (NSAIDs, ciprofloxacin, allopurinol, sulfonamide, cyclosporine).
3. Post renal:
   - Urethral—phimosis, paraphimosis, stricture, stone, blood clot, slaughed papilla.
   - Bladder neck—prostatic hypertrophy, malignancy, stone.
   - Bilateral ureteric—calculus, following surgery, pelvic tumor, uterine prolapse, retroperitoneal fibrosis (due to radiation, methysergide, idiopathic).

Q. What are the **causes** of CKD?

A. As follows:

- Glomerular diseases (30 to 40%), e.g. IgA nephropathy, MCGN
- Diabetes mellitus (20 to 40%)
- Hypertension (5 to 20%)
- Obstructive uropathy
- Chronic pyelonephritis
- Tubulointerstitial diseases (5 to 10%)
- Systemic inflammatory diseases (5 to 10%), e.g. SLE, vasculitis
- Renal artery stenosis (5%)
- Congenital and inherited (5%), e.g. polycystic kidney disease, Alport's syndrome
- Unknown (5 to 20%).

Q. What are the **clinical manifestations** of CKD?

A. As follows:

1. May be asymptomatic, until GFR falls below 30 mL/min/1.73 m^2 of body surface area. High urea and creatinine may be found on routine investigation, sometimes there may be hypertension, anemia, proteinuria on routine urine examination.
2. General features—early features may be nocturia, polyuria, anorexia, nausea, vomiting, diarrhea, weakness, malaise, insomnia, breathlessness on exertion, paresthesia, bone pain, edema, amenorrhea in woman, sexual dysfunction in man.
3. In ESRF—general features are more severe, and CNS symptoms may be more. Features like hiccup, pruritus, deep respiration (Kussmaul's respiration), muscular twitching, fit, drowsiness, even coma may occur.
4. Other features may be present, which may occur due to involvement of different systems of the body (see below).

Q. What are the different **features** due to involvement of different systems of the body?

A. CKD can involve any system of the body, symptoms and signs may develop according to the involvement:

1. Bone diseases (renal osteodystrophy):
   - Osteomalacia (or ricket called renal ricket)
   - Osteoporosis
   - Osteosclerosis (in vertebral body, giving rise to Rugger Jersey spine)
   - Osteitis fibrosa cystica.

2. Skin disease:
   - Pruritus—due to retention of nitrogenous waste products, hypercalcemia, hyperphosphatemia, hyperparathyroidism and iron deficiency. Patient on dialysis, inadequate dialysis may have pruritus due to unknown mechanism
   - Dry skin
   - Eczematous lesions, particularly near arteriovenous fistula
   - Ecchymosis in advanced disease due to increased bleeding tendency
   - Porphyria cutanea tarda (PCT) due to decreased hepatic uroporphyrinogen decarboxylase and decreased clearance of porphyrins in urine or by dialysis
   - Pseudoporphyria (features like PCT but without enzyme deficiency).
3. Gastrointestinal—anorexia, nausea, vomiting. Also there may be decreased gastric emptying, increased risk of reflux esophagitis, peptic ulceration, acute pancreatitis and constipation.
4. Metabolic abnormalities:
   - Hyponatremia, hyperkalemia or sometimes hypokalemia
   - Metabolic acidosis (due to increased tissue catabolism and retention of organic acids)
   - Hyperuricemia and gout
   - Hypocalcemia, hyperphosphatemia
   - Lipid abnormalities (hypercholesterolemia, hypertriglyceridemia).
5. Endocrine abnormalities:
   - Secondary hyperparathyroidism, may be tertiary
   - Prolonged half-life of insulin, due to reduced tubular metabolism of insulin. Also, insulin requirement in a diabetic patient decreases. But in advanced CKD, there may be end organ resistance to insulin, leading to impaired glucose tolerance
   - Hyperprolactinemia (presents with galactorrhea in men as well as women, loss of libido and sexual dysfunction in both sexes).
   - Others—increased LH, decreased serum testosterone (erectile dysfunction, decreased spermatogenesis), oligomenorrhea or amenorrhea (in female), impaired growth in children, abnormal thyroid hormone levels (hypothyroid feature), partly because of altered protein binding.
6. Muscle dysfunction:
   - Generalized myopathy (due to the combination of poor nutrition, vitamin D deficiency, electrolyte abnormalities, hyperparathyroidism)
   - Muscle cramps
   - Restless leg syndrome.
7. Nervous system:
   - Peripheral nervous system:
     i. Polyneuropathy—both motor and sensory. Improves or resolve with dialysis
     ii. Median nerve compression in the carpal tunnel due to β 2 microglobulin related amyloidosis
     iii. Restless leg syndrome.
   - Central nervous system:
     i. Clouding of consciousness, convulsion, coma
     ii. Asterixis (flapping tremor)
     iii. Tremor
     iv. Myoclonus
     v. Dialysis disequlibrium syndrome
     vi. Dialysis dementia
     vii. Psychiatric problems—(anxiety, depression, phobia, psychosis)
     viii. CVD secondary to hypertension.

- Autonomic dysfunction:
  i. Postural hypotension
  ii. Fixed heart rate
  iii. Urinary retention or incontinence
  iv. Constipation
  v. Impotence
  vi. Pupillary constriction
  vii. Gustatory sweating
  viii. Anhydrosis.

8. Calciphylaxis (calcific uremic arteriolopathy)—rare but life threatening
9. Cardiovascular:
   - Hypertension
   - Cardiac failure
   - Pericarditis, pericardial effusion or tamponade, chronic constrictive pericarditis
   - Uremic cardiomyopathy
   - Increased atherosclerosis
   - Left ventricular hypertrophy is common in ESRF, even arrhythmia leading to death may occur
   - Systolic dysfunction due to myocardial fibrosis, abnormal myocyte function due to uremia, calcium overload and hyperparathyroidism, carnitine and selenium deficiency
   - Coronary artery calcification.
10. Respiratory—pulmonary edema (uremic lung) due to fluid overload
11. Malignancy—incidence is increased in CKD (RCC)
12. Nephrogenic systemic fibrosis—seen in patients with moderate to severe CKD, particularly those on dialysis. There is skin involvement with plaques, papules and nodules. The affected skin becomes thick, firm and assume a peau d'orange appearance. There is also muscle stiffness, joint contracture and fibrosis of lungs, pleura, diaphragm, myocardium, pericardium and dura mater. Probably Gadolinium containing contrast agent is responsible for this.

Q. What are the **stages** of CKD?

A. As follows:

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60 to 89
3	Moderate ↓ GFR A&B	30 to 59 (**A:** 45 to 59, **B:** 30 to 44)
4	Severe ↓ GFR	15 to 29
5	Kidney failure	< 15 (or dialysis)

Q. What are the **causes of anemia** in CKD?

A. Anemia is common in CKD, correlates with the severity of renal failure. It is usually normocytic and normochromic. The mechanisms are:

- Erythropoietin deficiency (most significant)
- Diminished erythropoiesis due to toxic effects of uremia on bone marrow suppression. Also by PTH, ACE inhibitor
- Reduced dietary intake and absorption of hematinics (iron, vitamin B12, folic acid)
- Increased red cell destruction (may also be during hemodialysis due to mechanical, oxidant and thermal damage)

- Increased blood loss due to capillary fragility, poor platelet function, occult gastrointestinal bleeding and blood loss during hemodialysis
- Erythropoietin alpha therapy may cause anemia (by pure red cell aplasia).

Note Remember the following:

- Anemia is less severe or absent in polycystic kidney disease, as erythropoietin is relatively more in this case
- In CKD, the patient can tolerate mild to moderate anemia, because there is more release of oxygen from hemoglobin. The mechanisms are—in CKD patient, there is acidosis and high 2, 3 DPG level in RBC, which shifts the oxygen dissociation curve to the right and more oxygen is released from hemoglobin. So, the patient doesn't require blood transfusion in mild to moderate anemia. Target hemoglobin is 11 to 12.5 g/dL.
- Anemia becomes obvious in stage B CKD.

Q. What is **renal osteodystrophy**?

A. This is a group of metabolic bone disease secondary to chronic renal failure and comprises the following:

- Osteomalacia (or ricket, called renal ricket)
- Osteoporosis
- Osteosclerosis (in vertebral body, giving rise to Rugger jersey spine)
- Osteitis fibrosa cystica.

Note Remember the following:

There may be adynamic bone disease in which bone formation and resorption are both depressed. Cause is unknown, may cause spontaneous fracture. There may be hypercalcemia, normal alkaline phosphatase, PTH is low, dual X-ray absorptiometry shows osteopenia. No proven treatment.

Q. What are the **mechanisms** of renal osteodystrophy?

A. As follows:

- Osteomalacia is secondary to deficiency of 1, 25-dihydroxycholecalciferol as kidney is unable to convert 25 hydroxycholecalciferol to 1,25 dihydroxycholecalciferol, due to deficiency of 1 α-hydroxylase enzyme
- Osteoporosis, though its mechanism is unknown, may be due to secondary hyperparathyroidism and hypocalcemia, also probably due to malnutrition
- Osteosclerosis—due to hyperparathyroidism which causes increased bone density, particularly seen in the spine in which there is bands of sclerosis in the margin and porotic bone in between, giving rise to Rugger jersey spine
- Osteitis fibrosa cystica—due to secondary hyperparathyroidism.

Q. How to **treat** renal osteodystrophy?

A. As follows:

- Treatment of renal failure
- Calcium supplement
- 1-α hydroxylated synthetic analog of vitamin D (active vitamin D).

Q. How to **treat CKD**?

A. As follows:

1. General measures:
   - Fluid restriction

- Salt restriction
- Protein restriction (0.5 g/kg body weight/day). However, this is controversial. Severe protein restriction is avoided. Excess consumption of protein should be avoided
- Smoking should be stopped
- Social and psychological support.

2. Symptomatic and supportive:
   a. Hypertension: Good control of blood pressure delays renal deterioration. Target control of BP is 130/80 mm Hg (if UTP < 1g/day) and 125/75 mm Hg (if UTP > 1g/day)
      - ACE inhibitor, increased to maximum dose
      - ARB is added, if goal is not achieved (in case of type 2 DM, treatment should be started with ARB)
      - Diuretic to prevent hyperkalemia and to help control BP. High and single dose is preferable
      - Calcium channel blocker (verapamil or diltiazem), added if goal is not achieved.

   b. Statins for dyslipidemia
   c. Hyperkalemia:
      - Dietary restriction of potassium intake (fruits like banana, orange, coconut, etc)
      - Drugs causing potassium retention should be stopped. (e.g. ACEI, ARB, spironolactone, ciclosporin)
      - Injection 10% calcium gluconate 10 cc over 5 minutes, may be repeated (it is cardio-protective, provides protection for 2 hours)
      - Glucose and insulin (50 mL of 50% glucose I/V + injection insulin 10 units), may be repeated
      - Correction of acidosis (if pH < 6.9, Inj. sodi-bi-carb 7.5% I/V, 50 to 100 mL daily for 3 days)
      - Occasionally, ion exchange resins may be needed (calcium resonium powder 15 g in 1 cup water to be taken orally. If the patient is unconscious, it may be given as enema, which is more effective then oral route)
      - If all fails or hyperkalemia is severe, hemodialysis or peritoneal dialysis may be needed.

   d. Acidosis:
      - Sodium bicarbonate (1.26%, IV) or calcium carbonate (upto 3 g/day). Bicarbonate should be maintained above 22 mmol/L.

   e. Calcium and phosphate control and suppression of PTH:
      - Hypocalcemia should be treated with calcitriol or alpha-calcidol and calcium supplementation. Serum calcium should be monitored frequently to avoid hypercalcemia.
      - For hyperphosphatemia—dietary restriction of phosphate containing food (milk, cheese, eggs) and phosphate binding drugs like calcium carbonate, aluminium hydroxide and lanthanum carbonate may be used with food to prevent phosphate absorption. Polymer based phosphate binders may be used.

   f. Anemia:
      - Synthetic (recombinant) human erythropoietin (EPO). Side effects are hypertension and thrombosis (may occur in arteriovenous fistula, used for hemodialysis)
      - If there is no response after 300 IU/kg weekly, or a fall in hemoglobin after a satisfactory response, then erythropoietin is likely to be ineffective, which may be due to iron deficiency, bleeding, infection, malignancy, formation of anti-EPO antibody or aluminum overload that occur in dialysis. These should be searched and treated. If iron is needed, it should be given intravenously.
      - Blood transfusion may be given in severe anemia. Risk of blood transfusion in CKD patient—fluid overload, potassium overload, increased chance of graft rejection after kidney transplant, so blood transfusion is better to be avoided. In severe anemia, BT should be given during hemodyalisis.

g. Male erectile dysfunction:
   - Testosterone deficiency should be corrected
   - Phosphodiesterase inhibitors like sildenafil may be used.

3. Definitive treatment of CKD – renal replacement therapy may be given, such as:
   - Hemodialysis
   - Hemofiltraiton
   - Peritoneal dialysis
   - Renal transplantation.
4. Treatment of primary cause, if any:
   - Diabetis melitus—insulin
   - Hypertension—antihypertensive
   - APKD—sirolimus decreases the cyst size
   - Removal of obstruction in obstructive uropathy.

Q. What are the **reversible factors** in CKD?

A. As follows:
- Hypertension
- Reduced renal perfusion, such as—renal artery stenosis, hypotension due to drug treatment, sodium and water depletion, poor cardiac function
- Urinary tract infection
- Urinary tract obstruction
- Other systemic infections that causes increased catabolism and urea production
- Nephrotoxic drugs.

Q. What are the indications of **urgent dialysis**?

A. As follows:
- Severe hyperkalemia
- Pulmonary edema or severe fluid overload
- Severe metabolic acidosis
- Uremic pericarditis
- Uremic encephalopathy
- Toxicity with a dialyzable poison (methanol, barbiturate, etc.)
- Recurrent vomiting due to uremia.

Q. What are the **indications** of renal replacement therapy?

A. As follows:
- Serum creatinine > 600 to 800 µmol/L (7 to 9 mg/dL), or e.GFR< 8 to 10
- Hyperkalemia (plasma potassium > 6 mmol/L despite medical treatment)
- Metabolic acidosis (H^+ > 56 nmol/L, pH < 7.25), HCO_3< 10 mmol/L
- Fluid overload and pulmonary edema
- Uremic pericarditis or encephalopathy
- Sepsis (tentative evidence for mediator removal), CRRT (continuous renal replacement therapy).

READ THE FOLLOWING TOPICS

Hemodialysis

Complications:

- Hypotension during dialysis due to fluid removal and hypovolemia. There may be chest pain and leg cramps

- Cardiac arrhythmia due to potassium and acid base shift
- Hemorrhage due to anticoagulation. Also, venous needle disconnection may lead to hemorrhage
- Anaphylactic reaction
- Sepsis, usually involving vascular access devices
- Pulmonary edema due to fluid overload
- Hemolytic reactions
- Air embolism
- Hard water syndrome
- Dialysis disequilibrium due to rapid correction of uremia.

Contraindication of HD:

- CCF with low EF%
- Generalized atherosclerosis with poor vascular access for AVF.

(They are the ideal candidate for peritoneal dialysis).

Peritoneal Dialysis

Complications:

- Peritonitis due to infection
- Infection around the catheter site
- Constipation
- Massive pleural effusion (dialysate leak through a diaphragmatic defect into the thoracic cavity). Dialysate may leak into the scrotum down through a patent processus vaginalis
- Failure of peritoneal membrane function due to long-term CAPD
- Sclerosing peritonitis (potentially fatal).

Contraindications:

- Previous peritonitis causing peritoneal adhesions
- Presence of a stoma (e.g. colostomy)
- Active intra-abdominal sepsis (absolute contraindication)
- Abdominal hernia
- Co-morbidities like coronary artery disease, congestive cardiac failure.

Q. What are the **complications** of long-term dialysis?

A. As follows:

- Cardiovascular disease
- Sepsis (leading cause of death in long term dialysis patient)
- Dialysis associated ascites
- Dialysis amyloidosis
- Dialysis associated arthropathy.

Renal transplantation is the treatment of choice for ESRD.

Q. What are the **contraindications** of renal transplantation?

A. As follows:

1. Absolute:
   - Active malignancy – a period of at least 2 years of complete remission recommended for most tumors

- Active vasculitis or recent anti GBM disease
- Severe heart disease or any severe co-morbid condition
- Severe occlusive aorto-iliac vascular disease.

2. Relative:
   - Age—while practice varies, transplants are not routinely offered to very young children (< 1 year) or older people (>75 years)
   - High risk of disease recurrence in the transplant kidney
   - Disease of the lower urinary tract—in patients with impaired bladder function, stricture urethra (ileal conduit may be considered.)
   - Significant co-morbidity.

Q. What drugs are used to **prevent rejection**?

A. Usually a combination of:

- Cyclosporine or tacrolimus
- Azathioprine or mycophenolate mofetil/ sirulimus or evanolimus
- Prednisolone.

Q. What are the **complications** after renal transplantation?

A. As follows:

- Acute rejection
- Chronic rejection
- Infection—CMV, pneumocystis jiroveci, oral candidiasis, polioma virus. Bacterial infection is common in first few months
- Complication of immunosuppressive drugs including steroid
- Acute tubular necrosis (ATN)—it is the most common cause of cadaveric graft dysfunction (40 to 50%). It is associated with a worse long-term outcome and predisposes to rejection.
- Technical failures—occlusion or stenosis of the arterial anastomosis, occlusion of the venous anastomosis and urinary leaks
- Post transplantation lymphoproliferative disorder—EBV associated malignancies (such as lymphoma) are common in patients who received biological agents and in children
- Chronic allograft nephropathy—most common cause of late graft failure
- Malignancy—skin tumor (including basal and squamous cell carcinoma), renal, cervical and vaginal
- Hypertension
- Atherosclerosis
- Recurrence of renal disease.

Complication of Renal transplantation (Remember the formula— 'TROPICAL'):

- **T**–Thrombosis of graft kidney artery and vein
- **R**–Rejection of graft kidney
- **O**–Obstruction of graft ureter with perinephric hematoma, seroma, urinoma, or lymphocele
- **P**–Primary disease recurrence. The most common recurrence is MCGN type II (80 to 100%)
- **I**–Infection which may be bacterial (any, TB), Viral (CMV, chicken pox, polioma virus), fungal, (*Cryptococcuus neoformans*), Parasite (*Pneumocystis Jiroveci*, ispspora cycloporium , microspora, Giardia)
- **C**–ciclosporine toxicity and other imunosupressive drugs toxicities
- **A**–Acute tubular necrosis
- **L**–Leakage of graft ureter due to error or ischemia.

Q. What is **acute rejection**?

A. Acute rejection characterized by rising of creatinine, fever, loin pain, hypertension, swelling of the graft. Urine shows protein, lymphocyte, and renal tubular cells. Occurs in 10 to 30% cases within 6 months. Graft biopsy shows immune cell infiltrate and tubular damage.

Treatment—high dose methylprednisolone, resistant cases may require antithymocyte globulin or ALG or OKT3 may be used.

Q. What is **chronic rejection**?

A. It occurs usually after 6 months. The patient presents with gradual rise of creatinine and proteinuria. Graft biopsy shows vascular change, fibrosis and tubular atrophy. It is not responsive to increased immunosuppression.

HYPERTENSION WITH CKD

CHIEF COMPLAINTS

- Frequency of micturition for … months
- Excessive thirst, weakness and palpitation for … months
- Anorexia, nausea and occasional vomiting for … months.

HISTORY

History of present illness: The patient was alright about … years back. Then she noticed swelling of the face and legs, associated with scanty micturition, increased thirst, palpitation and weakness for which she consulted with local doctor. After evaluation, she was diagnosed as a case of kidney disease and referred to nephrologist. She was hospitalized and thorough investigation was done including renal biopsy from left kidney. While she was in the hospital, treatment with prednisolone and ranitidine were given, continued for 6 months. With this treatment, the patient was feeling better. 2 years later, she again developed same type of illness. Her weakness is increasing, which is associated with severe loss of appetite followed by occasional vomiting. She denies any history of fever, abdominal pain, loin pain or burning during micturition. With this problem , she was admitted in the hospital.

After evaluation, she was found having severe renal failure, hypertension, severe anemia. Emergency dialysis was given along with blood transfusion. Subsequently an arterio-venous fistula was made in the left forearm. Now patient is on regular hemodialysis 3 session per week.

History of past illness: There is no history of diabetes mellitus or hypertension or any infection prior to her present illness.

Family history: There is no such illness in the family.

Personal history: Mention according to the patient's statement.

Socioeconomic history: Mention according to the patient's statement.

Drug history: She did not take any drug that may be responsible for such illness.

GENERAL EXAMINATION

- Ill looking, puffy face and depressed looking
- Moderately anemic
- Edema—present, pitting
- Nail—half and half nail**,** no clubbing
- No jaundice, cyanosis
- No lymphadenopathy or thyromegaly
- Pulse—110/min
- BP—200/110 mm Hg
- Skin—dry, there are multiple scratch mark.

SYSTEMIC EXAMINATION

Gastrointestinal System

Lip, gum, tongue, oral cavity—looks pale.

Abdomen

1. **Inspection:** No abnormality detected.
2. **Palpation:**
   - No organomegaly
   - Kidneys are not ballotable
   - Fluid thrill—absent
   - There is no tenderness over the renal angle.
3. **Percussion:** Shifting dullness is absent.
4. **Auscultation:** No renal bruit.

Nervous System

All findings like HPF, motor, sensory, etc. are normal. Fundoscopy shows - Bilateral papilloedema present.

Examination of the other systems reveals no abnormalities.

Bedside urine for protein: (++) or (+++)

SALIENT FEATURES

Mrs … 40 years old, housewife, nondiabetic, nonsmoker, hailing from …was hospitalized with frequency of micturition, excessive thirst, weakness and palpitation ,anorexia, nausea and occasional vomiting for … months.

The patient was alright about … years back. Then she noticed swelling of the face and legs, associated with scanty micturition, increased thirst, palpitation and weakness for which she consulted with local doctor. After evaluation, she was diagnosed as a case of kidney disease and referred to nephrologist. She was hospitalized and thorough investigation was done including renal biopsy from left kidney. While she was in the hospital, treatment with prednisolone and ranitidine were given, continued for 6 months. With this treatment, the patient was feeling better. About 2 years later, she again developed same type of illness. Her weakness is increasing, which is associated with severe loss of appetite followed by occasional vomiting. She denies any history of fever, abdominal pain, loin pain or burning during micturition. With this problem, she was admitted in the hospital.

After evaluation, she was found having severe renal failure, hypertension, severe anemia. Emergency dialysis was given along with blood transfusion. Subsequently an arterio-venous fistula was made in the left forearm. Now patient is on regular hemodialysis 3 sessions per week.

On Examination—
General examination (mention as above).
Systemic examination (mention as above).

My diagnosis is hypertension with CKD (stage v) on maintenance hemodialysis.

Q. What is your **differential** diagnosis?

A. Chronic pyelonephritis.

Q. What **investigations** should be done in this case?

A. As follows:

1. Urine analysis:
   - Low and fixed specific gravity (around 1.010)

- Albuminuria may be present. RBC, WBC
- Granular casts may be present.

2. CBC and PBF examination (shows normocytic, normochromic anemia)
3. Renal function tests (blood urea and serum creatinine are high)
4. Creatinine clearance (important to assess the severity of renal failure)
5. Serum electrolytes, calcium and phosphate (shows hypocalcemia, hyperphosphatemia, hyperkalemia and reduced bicarbonate level).
6. Serum uric acid (may be high).
7. Plain X-ray abdomen (shows the presence of any obstructive uropathy, may also show the kidney size).
8. USG of the whole abdomen (typically shows bilateral contracted kidney. Kidneys may be enlarge or normal in size in diabetic glomerulosclerosis, amyloidosis, polycystic kidney diseases, bilateral hydronephrosis and myeloma kidney).
9. CT scan of abdomen.

Q. What are the **types** of glomerulonephritis?

A. It may be primary or secondary:

1. **Primary:**
   - Minimal change
   - Membranous
   - Proliferative:
     a. Post-streptococcal (and after other infection)
     b. Mesangiocapillary
     c. Crescentic
     d. Mesangial proliferative
   - IgA nephropathy
   - Focal segmental glomerulosclerosis. (FSGS).
2. **Secondary to systemic disease:**
   - Systemic lupus erythromatosis (SLE)
   - Wegener's granulomatosis
   - Polyarteritis nodosa (PAN)
   - Goodpasture's syndrome
   - Honoch-Schonlein purpura
   - Infective endocarditis
   - Cryoglobulinemia with or without hepatitis C
   - Multiple myeloma.

Q. What is the **treatment** of CGN?

A. If any cause is identified, it should be treated. Other treatment as in CRF.

BRIEF NOTES ABOUT BERGER'S IGA NEPHROPATHY

Definition: It is a type of immune complex mediated focal and segmental proliferative glomerulonephritis with mesangial deposition of IgA. In some cases, IgG, IgM, C_3 may be deposited in mesangium. It is the most common form of glomerulonephritis.

Presentation: It is common in children and young adults. Males are 2 to 3 times more affected than female. Most patients usually present with recurrent microscopic or even gross hematuria. It may follow a viral respiratory or GIT infection or flu like illness. Hematuria is universal, proteinuria is usual and hypertension is common, 5% may develop nephrotic syndrome. In some cases, progressive

loss of renal function, leading to end stage renal failure (20%) in 20 years. IgA nephropathy may be associated with hepatic cirrhosis, celiac disease, HIV and CMV infection.

It may be confused with Henoch-Schonlein purpura (HSP). IgA nephropathy causes only kidney. HSP causes systemic disease involving skin, gut, kidney and joints.

Investigations:

- Serum IgA—high in upto 50% (serum complements are usually normal)
- Immune complex estimation
- Kidney biopsy shows focal proliferative glomerulonephritis with diffuse mesangial IgA deposit. In some cases, IgG, IgM, C_3 may be deposited in mesangium
- Skin biopsy often shows granular deposit of IgA in dermal capillaries of affected patients
- Other investigations—renal function tests, ultrasonogram of renal system

Treatment:

- Episodic attack resolves spontaneously
- Patient with proteinuria over 1 to 3 g/day, mild glomerular change and good renal function should be treated with steroid
- In progressive renal disease, prednisolone plus cyclophosphamide for 3 months, then prednisolone plus azathioprine
- Combination of ACE inhibitor and ARB should be given to all cases with or without hypertension or proteinuria
- Other treatment like fish oil may be beneficial
- Tonsillectomy may be helpful, if recurrent tonsillitis
- If the patient develops ends stage renal failure, kidney transplantation is an excellent option. Recurrence of the disease may occur in 30% cases in 5 to 10 years in post-transplant.

Prognosis: Complete remission is uncommon. Prognosis is usually good, renal failure is uncommon. Bad prognostic factors are:

- Proteinuria > 1 g/day
- Others—hypertension, persistent microscopic hematuria and proteinuria, glomerulosclerosis and abnormal kidney function.

Q. What are the diseases **associated** with IgA deposit in kidney?

A. As follows:

- IgA nephropathy
- Henoch-Schonlein purpura
- Chronic liver disease
- Malignancy like bronchial carcinoma
- Seronegative spondyloarthropathy
- Coeliac disease
- Mycosis fungoides
- Psoriasis.

BRIEF NOTES ABOUT GOODPASTURE'S SYNDROME

Definition: Goodpasture's syndrome is a clinical syndrome of glomerulonephritis and pulmonary hemorrhage, mediated by anti-GBM antibody.

Clinical presentations: Goodpasture's syndrome is 6 times more in males, age 20 to 40 years. Females are affected more, if it occurs after the age of 60. Onset is preceded by upper respiratory

tract infection. Patient presents with cough, hemoptysis and glomerulonephritis or renal failure. In one-third cases, only glomerulonephritis is present, no lung injury. Lung hemorrhage is more in smokers. Systemic features like fever, malaise, arthritis, headache, weight loss are not common, but may occur. Hypertension is usually not a feature. Chest pain and pleurisy are also rare.

Differential diagnoses: In young patient with renal and lung involvement, the most common cause is Goodpasture's syndrome. Other causes are:

- Microscopic polyangitis (MPA)
- Wegener's granulomatosis
- SLE
- In elderly, bronchial carcinoma with metastasis in the kidney or membranous glomerulonephritis may occur.

Investigations:

- CBC and ESR
- Chest X-ray (shows lung infiltrate due to hemorrhage)
- P-ANCA (positive in 30%) and C-ANCA
- ANA is negative and complements are normal
- Anti-GBM antibody is positive in 90% cases (usually IgG, occasionally IgA or IgM)
- Lung function test (shows increased CO transfer due to pulmonary hemorrhage and restrictive lung disease may occur in advanced stage. Associated influenza A_2 virus may be found).
- In sputum, hemosiderin-laden macrophage may be present.
- Kidney biopsy (it shows proliferative or crescentic glomerulonephritis. Immunofluorescence shows anti-GBM antibody deposition in a linear pattern).

Treatment:

- Plasmapheresis plus methylprednisolone (1 to 2 g/day for 3 days), followed by oral prednisolone (1 mg/kg/day)
- Cyclophosphamide 2 to 3 mg/kg/day or IV 0.5 to 1 g/m^2 surface area, every month may be given
- Dialysis may be needed in renal failure
- Sometimes, kidney transplantation may be considered. Recurrence may occur in transplantated kidney.

LUPUS NEPHRITIS

CHIEF COMPLAINTS

- Pain in different large and small joints for.... months
- Swelling of lower limbs and scrotum for.... month.

HISTORY

History of present illness: Mr … a young man of 28 was admitted in the hospital on … with the complaints of pain in different large and small joints for .... months, swelling of lower limbs and scrotum for 1 month.

According to statement of patient, he was alright .... months back. Since then, he has been suffering from pain and swelling of both knee joints, subsequently involving the ankle, elbow and small joints of limbs. Pain is more with activity and reduces with rest. He also noticed morning stiffness, usually persist 2 to 3 hours, reduces with some exercise.

For the last .... month, the patient noticed swelling of both lower limbs and scrotum, which is gradually increasing. There is also passage of scanty reddish urine. He consulted with a local physician, who prescribed tablet frusemide and ciprofloxacin, but no improvement. His swelling both lower limbs was increasing and after a week, the patient was admitted in the hospital. 2 days after admission, the patient is complaining of high fever with chills and rigor, associated with right loin pain, which is dull ache in nature, no radiation.

On enquiry, there is no history of purulent urethral discharge, bloody dysentery, skin rash and mouth ulcer.

History of past illness: The patient suffered from occasional low grade fever, pain in multiple joints for few months back.

Family history: All the family member are in good health, there is no such illness in the family.

Personal history: He is married and has a kid, non smoker, non alcoholic.

Socioeconomic history: He comes from a middle class family, lives in a brick built house with good sanitation and water supply.

Drug history: He took frusemide tablets and some antibiotics as prescribed by the local physician.

GENERAL EXAMINATION

- The patient is ill looking, edematous and pale
- Pitting edema is present
- Mildly anemic
- No clubbing, jaundice, cyanosis, koilonychia but leukonychia involving all the nails of fingers and toes is present
- No lymphadenopathy or thyromegaly
- Pulse—80/min regular in rhythms
- BP—90/75 mm Hg
- Temperature—103ºF.

SYSTEMIC EXAMINATION

Gastrointestinal System

Lips, gum, tongue, oral cavity—normal. There is one small ulcer on inner side of mouth.

Abdomen

1. **Inspection:**
   - Generalized distension of abdomen, umbilicus is everted
   - Scrotum is grossly swollen
2. **Palpation:**
   - No organomegaly
   - Kidneys are not ballotable
   - Fluid thrill—present
   - Tenderness is present over the renal angle
3. **Percussion:** Shifting dullness present
4. **Auscultation:** No abnormality.

Examination of the other systems reveals no abnormalities.

Bedside urine: protein+, sugar nil.

SALIENT FEATURES

Mr … a young man of 28 was admitted in the hospital on … with the complaints of pain in different large and small joints for .... months, swelling of lower limbs and scrotum for 1 month.

According to statement of patient, he was alright .... months back. Since then, he has been suffering from pain and swelling of both knee joints, subsequently involving the ankle, elbow and small joints of limbs. Pain is more with activity and reduces with rest. He also noticed morning stiffness, usually persist 2 to 3 hours, reduces with some exercise.

For the last .... month, the patient noticed swelling of both lower limbs and scrotum, which is gradually increasing. There is also passage of scanty reddish urine. He consulted with a local physician, who prescribed tablet frusemide and ciprofloxacin, but no improvement. His swelling both lower limbs was increasing and after a week, the patient was admitted in the hospital. About 2 days after admission, the patient is complaining of high fever with chills and rigor, associated with right loin pain, which is dull ache in nature, no radiation.

On enquiry, there is no history of purulent urethral discharge, bloody dysentery, skin rash and mouth ulcer.

In his past medical history, the patient suffered from occasional low grade fever, pain in multiple joints for few months back.

There is no family history of such illness. He used to take vitamins prescribed by local doctors.

On Examination—

General examination (mention as above).
Systemic examination (mention as above).
Urine shows gross proteinuria.

My diagnosis is Glomerulonephritis, which may be due to SLE, rheumatoid arthritis.

Q. Why it is **SLE** ?

A. As there is history of polyarthritis, mouth ulcer.

For details of renal lupus (see rheumatology chapter)

Q. What **investigations** should be done in this case?

A. As follows:

1. CBC and ESR
2. Urine R/M/E (albuminuria, granular casts may be present)
3. Renal function test (blood urea and creatinine)
4. Creatinine clearance (important to assess the severity of renal failure)
5. Serum electrolytes, calcium and phosphate
6. Serum uric acid (may be high)
7. ANA and anti-ds DNA, C_3 and C_4
8. Others:
   - Plain X-ray abdomen
   - USG of the whole abdomen
   - CT scan of abdomen (in some case)
   - Transcutaneous renal biopsy.

Q. What is the **typical renal problem** in SLE?

A. Proliferative glomerulonephritis, which is characterized by hematuria, proteinuria and casts on routine urine microscope.

Renal involvement in SLE occurs in 30% case. Of these, 25% will develop end stage renal failure within 10 years. All patients of SLE should have regular screening of urine for blood and protein. Asymptomatic patient with proteinuria may be the early stage and treatment may prevent the progression of renal impairment. Renal vein thrombosis may occur in antiphospholipid syndrome.

Treatment:

- Depends on clinical presentation and type. Definitive histological diagnosis is essential.
- Type I—no treatment, only follow up.
- Type II—usually benign. Some patients may need treatment.
- Type III, IV and V—immunosuppressive therapy with steroid and cyclophosphamide or mycophenolate mofetil are used for induction. Then azathioprine and mycophenolate mofetil are used for maintenance.
- Rituximab (anti CD-20) may be used in some patient.
- Symptomatic treatment for hypertension and edema.

PUO IN HEMODIALYSIS PATIENT

CHIEF COMPLAINTS

- Fever for -----months
- Weakness and loss of appetite for … months
- Nausea and occasional vomiting for … months
- Swelling and puffiness of the face for … days.

HISTORY

History of present illness: Mrs … 40 years house wife, known case of diabetes mellitus for 10 years was diagnosed as case of CKD, and on regular hemodialysis. For the last … months, she has been suffering from fever, which is low grade continued, highest recorded temperature is 101°F. Fever is not associated with chill and rigor, subside only with paracetamol. She also complains of weakness, loss of appetite, nausea and occasional vomiting. Her bowel habit is normal. There is no history of joint pain, skin rash, cough or oral ulcer.

History of past illness: She is non-hypertensive, but diabetic for … years and used to take insulin.

Family history: There is no history of such illness in her family.

Personal history: Mention according to the patient's statement.

Socioeconomic history: Mention according to the patient's statement.

Drug history: She was treated with ceftriaxone, ceftazidime and vancomycin but no response.

GENERAL EXAMINATION

- The patient is ill looking, emaciated and pale
- Moderately anemic
- Pitting edema—present
- Skin is rough with some scratch mark in different parts of the body
- There is leukonychia (or half and half nail)
- No clubbing, jaundice, cyanosis or koilonychia
- No lymphadenopathy or thyromegaly
- Pulse—110/min
- BP—110/65 mm Hg (mention postural drop if present)
- Fistula for dialysis in the right hand.

SYSTEMIC EXAMINATION

Gastrointestinal System

Lip, gum, tongue, oral cavity—looks pale.

Abdomen

1. **Inspection:** No abnormality detected.
2. **Palpation:**
   - No organomegaly

- Kidneys are not ballotable
- Fluid thrill—absent
- There is no tenderness over the renal angle.

3. **Percussion:** Shifting dullness absent
4. **Auscultation:** No renal bruit.

CVS: Mention position of apex, carotid bruit.

Nervous System

Examined the sensory system, dorsal column lesion, reflexes (ankle jerk) and fundoscopy (diabetic retinopathy, hypertensive retinopathy).

Bedside urine examination: Sugar present, protein+++.

Daily urine output 500 mL/day

SALIENT FEATURES

Mrs … 40 years house wife, known case of diabetes mellitus for 10 years was diagnosed as case of CKD, and on regular hemodialysis. For the last … months, she has been suffering from fever, which is low grade continued, highest recorded temperature is 101°F. Fever is not associated with chill and rigor, subside only with paracetamol. She also complains of weakness, loss of appetite, nausea and occasional vomiting. Her bowel habit is normal. There is no history of joint pain, skin rash, cough or oral ulcer. There is no history of such illness in her family. She was treated ceftriaxone, ceftazidime and vancomycin but no response.

On Examination—
General examination (mention as above).
Systemic examination (mention as above).

My diagnosis is PUO with CKD on hemodialysis.

Q. What **investigations** do you suggest fever in CKD on hemodialysis?

A. As follows:

- Urine R/E and C/S
- CBC and PBF
- Blood for C/S
- CXR P/A view
- MT
- USG of the whole abdomen
- Echocardiography
- Anti-CMV antibody
- ANA and anti ds-DNA for SLE, screening for hepatitis B and C, HIV
- P-ANCA, C-ANCA
- Other investigations according to suspicion of cause—anti-toxoplasma antibody, anti-brucella antibody, antifungal antibody (for aspergiloma, histoplasma).

Q. What are the **causes** of fever in such case?

A. As follows:

- Tuberculosis
- Viral infection (commonly CMV)

- Collagen disease (SLE)
- Vasculitis (microscoic polyartaritis, Wegners granulomatosis).

Q. How will you treat a **tuberculosis patient with CKD**?

A. Rifampicin, INH and pyrazinamide are given in the usual dose. Only ethambutol 7.5 mg/kg body weight is given.

Q. How to **treat Tuberculosis in hemodialysis** patient**?**

A. Treatment is as above, but on the day of dialysis, anti-tubercular drug should be given after the dialysis.

Q. How to **treat CMV** infection?

A. IV Gancyclovir is used in the following dose:

- Induction: 5 mg/kg every 12 hourly for 14 to 21 days.
- Maintenance: 5 mg/kg once daily for 7 days per week or 6 mg/kg once daily for 5 days per week. Dose to be given by IV infusion.
- In patients with renal impairment getting dialysis: 1.25 mg/kg for induction and 0.625 mg/kg for maintenance, to be given post-dialysis on days when dialysis is performed.

CrCl (mL/min)	Dosage Recommendation	
	Induction	Maintenance
» ≥70	5 mg/kg every 12 hours	5 mg/kg every 24 hours
» 50 to 69	2.5 mg/kg every 12 hours	2.5 mg/kg every 24 hours
» 25 to 49	2.5 mg/kg every 24 hours	1.25 mg/kg every 24 hours
» 10 to 24	1.25 mg/kg every 24 hours	0.625 mg/kg every 24 hours

CHAPTER 7

Rheumatology

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- Hemophilic Arthritis 460

SYSTEMIC LUPUS ERYTHEMATOSUS

CHIEF COMPLAINTS

- Pain in multiple joints for … months
- Skin rash for … months
- Fever for … months
- Weight and hair loss for … months
- Oral ulcer for … months.

HISTORY

History of present illness: According to the statement of the patient, she was reasonably well … months back. Since then, she has been suffering from pain in multiple small and large joints of both upper and lower limbs, predominantly lower limbs, mostly involving the hands, wrists, knees, ankles and small joints of feet. The pain persists throughout day and night, more marked in the morning, associated with morning stiffness, and not relieved by rest, but reduces with pain-killers. She also noticed skin rashes on the face, arms and legs for the last … months that are aggravated on exposure to sunlight. The patient also complains of low grade continued fever for the last … months, highest recorded temperature is 100ºF. Fever is not associated with chills and rigors, subsides by taking paracetamol. There is no history of night sweats. The patient also complains of marked loss of weight and weakness. She noticed some loss of scalp hair and painless mouth ulcer. There is no history of spontaneous abortion, bleeding, venous thrombosis, convulsion, unconsciousness, dryness of the mouth or eyes, pain in abdomen, dysuria, edema, Raynaud's phenomenon, gangrene or cough. Her bowel and bladder habits are normal.

History of past illness: Nothing significant.

Drug history: There is no history of taking OCP or other drugs.

Family history: There is no similar illness in her family. Her parents and two sisters are in good health.

Personal history: Mention according to the patient's statement.

Socioeconomic history: Mention according to the patient's statement.

Menstrual history: The patient complains of occasional irregular menstruation, sometimes associated with menorrhagia.

GENERAL EXAMINATION

- Ill looking and emaciated.
- Alopecia is present on the scalp.
- Butterfly rash is present on the face over the cheek, nasal bridge, sparing the nasolabial folds that are fixed, erythematous, some are flat, some are raised. Also, maculopapular skin rashes are present on the dorsum of the hands and legs, some of these are pigmented and scaly.
- Oral ulcer present on inner side of lips and cheeks, some are coated with whitish discharge and has irregular margin.
- Moderately anemic.
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema.

- No lymphadenopathy or thyromegaly.
- Pulse: 88/min.
- BP: 90/40 mm Hg.
- Temperature: 99^0 F.

Musculoskeletal system:

- Both knee and ankle joints are slightly swollen and tender
- Wrist, MCP and IP joints of both hands—slightly swollen and tender, but no deformity.

Gastrointestinal system: No abnormality detected (liver and spleen may be palpable, mention if any).

Eyes: No abnormality detected.

Respiratory system: No abnormality detected.

Cardiovascular system: No abnormality detected.

Nervous system: No abnormality detected.

Bedside urine examination: Normal (or proteinuria, mention if present).

SALIENT FEATURES

Ms. …, 33 years, housewife, normotensive, nondiabetic, nonsmoker, hailing from …, presented with pain in multiple small and large joints of both upper and lower limbs for … months. The pain involves predominantly lower limbs, mostly the hands, wrists, knees, ankles and small joints of feet. The pain persists throughout day and night, more marked in the morning, associated with morning stiffness, and not relieved by rest, but reduces with pain-killers. She also noticed skin rashes on the face, arms and legs for the last … months that are aggravated on exposure to sunlight. The patient also complains of low grade continued fever for the last … months, highest recorded temperature is 100ºF. Fever is not associated with chills and rigors, subsides by taking paracetamol. There is no history of night sweats. The patient also complains of marked loss of weight and weakness. She noticed some loss of scalp hair and painless mouth ulcer. There is no history of spontaneous abortion, bleeding, venous thrombosis, convulsion, unconsciousness, dryness of the mouth or eyes, pain abdomen, dysuria, edema, Raynaud's phenomenon, gangrene or cough. Her bowel and bladder habits are normal. She complains of occasional irregular menstruation, sometimes associated with menorrhagia. There is no history of taking OCP or other drugs. There is no similar illness in her family. She was treated by local physicians by multiple drugs the name of that she could not mention.

On examination, general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is systemic lupus erythematosus.

Q. What are your **differential diagnoses?**

A. As follows:

- Dermatomyositis
- Mixed connective tissue disease (MCTD)
- Sarcoidosis
- Rheumatoid arthritis.

Q. Why not **rheumatoid arthritis?**

A. Because in this case, there are multiple skin rash and butterfly rash and there is no deformity of the involved joints.

Q. What **investigations** should be done in SLE?

A. As follows:

1. CBC (anemia, leukopenia, thrombocytopenia, lymphopenia and high ESR)
2. Urine (proteinuria, hematuria, and RBC or granular cast). If proteinuria is present, 24 hours urinary protein should be done
3. CRP (It is normal. If CRP is increased, it indicates infection)
4. Antinuclear antibody **(**ANA) (positive in 95% cases. It is the most sensitive screening test)
5. Anti-double-stranded DNA (positive in 30% to 50% of the cases. It is highly specific for SLE)
6. Anti-Sm (Smith) antibody (positive in 10% to 25% cases)
7. Complements (C3 and C4 are low in active disease)
8. Immunoglobulin (high titer of IgM and IgG)
9. Serum anti-phospholipid antibody
10. Others (these indicate presence of antiphospholipid antibody):
    - Venereal disease research laboratory (VDRL) (false positive)
    - Platelet (low)
    - Prothrombin time (prolonged)
    - Activated partial thromboplastin time (APTT) (prolonged, not corrected by addition of normal plasma)
11. Skin biopsy (from normal skin and skin lesion for histopathology and DIF):
    - Normal skin biopsy—immunofluorescence test shows deposition of immune complex at dermoepidermal junction (lupus band). Biopsy specimen of normal skin for DIF should be sent in normal saline soaked gauge (not in formalin, as the protein is denatured by formalin). For histopathology, biopsy specimen is taken in formalin
12. If renal involvement—24 hours urinary protein, serum urea and creatinine, creatinine clearance rate (CCR), renal biopsy
13. If CNS involvement—EEG, CT or MRI.

Q. What are the **antibodies** found in SLE?

A. As follows:

- ANA
- Anti-double-standard DNA
- Anti-Smith (more specific in SLE)
- Anti-Ro/La (responsible for congenital heart block in neonate)
- Antiphospholipid antibody/lupus anticoagulant (may cause repeated abortion, thrombocytopenia)
- Anti-histone (found in drug induced SLE)
- Anti-C_{1q} (it has prognostic significance in lupus nephritis).

Q. What are the **causes** of positive **ANA**?

A. As follows:

- SLE
- Sjogren syndrome
- Systemic sclerosis
- Dermatomyositis
- Polymyositis
- MCTD
- Autoimmune hepatitis
- Others—rheumatoid arthritis, autoimmune thyroid disease, vasculitis.

RELATED QUESTIONS AND ANSWERS

Q. What is **SLE?**

A. It is an autoimmune chronic multisystem disease characterized by production of multiple autoantibodies, immune complexes and widespread immune mediated organ damage.

Q. From where is the **name** SLE derived?

A. Lupus means wolf. SLE is named because of the erosive nature of the condition that looks like the damage caused by hungry wolf's bite.

Q. What are the **manifestations** of SLE?

A. SLE is more in females, F:M = 9:1, age in second and third decades. Sex ratio is equal in children and elderly. It involves any organ of the body.

1. General features:
- Fever
- Arthralgia, arthritis (non-erosive), myalgia
- Fatigue, tiredness, weakness, malaise
- Weight loss
- Skin manifestation (80%)—malar rash, discoid rash, photosensitivity, ulcer, vasculitic lesions on the finger tips and around the nail folds, livedo reticularis. (In discoid lupus, only skin is involved)
- Scarring alopecia. Lupus hair (short broken hair above the forehead).

2. Heart (involved in 25%):
- Pericarditis, pericardial effusion and myocarditis
- Rarely, non-infective endocarditis called Libman-Sacks endocarditis (common in anti-phospholipid syndrome). Mitral regurgitation may occur
- There is increased frequency of IHD and stroke in patients with SLE.

3. Vascular: Raynaud's phenomenon, vasculitis, arterial and venous thrombosis (in anti-phospholipid syndrome) and atherosclerosis.

4. Lungs (involved in up to 50% cases):
- Pleurisy, pleural effusion (may be bilateral) and pneumonitis
- Atelectasis and shrinking lung with elevation of diaphragm (shrinking lung syndrome)
- Pulmonary fibrosis (rare, found in overlap syndrome)
- Increased risk of thromboembolism
- Intrapulmonary hemorrhage with vasculitis (rare but dangerous).

5. Eyes:
- Episcleritis, scleritis, conjunctivitis and optic neuritis (blindness is uncommon)
- Secondary Sjögren's syndrome (dry eye and dry mouth) in 15% cases
- Retinal vasculitis can cause infarct (fundoscopy shows white, hard exudate called cytoid body).

6. Gastrointestinal tract (GIT) (rarely involved):
- Mouth ulcer (usually painless, but may be painful if secondary infection)
- Mesenteric vasculitis (causing small bowel infarction or perforation)
- Ascites
- Others—nausea, vomiting, diarrhea, abdominal pain, mild hepatosplenomegaly.

7. Hematological:
- Anemia (normocytic normochromic) and Coombs' positive autoimmune hemolytic anemia
- Thrombocytopenia (often confused with ITP), leukopenia, neutropenia and lymphopenia.

8. Central nervous system (CNS):
- Fatigue, headache, poor concentration

- Visual hallucination
- Chorea
- Epilepsy
- Migraine
- Cerebrovascular disease (CVD)
- Organic psychosis
- Paralysis
- Depression
- Transverse myelitis
- Lymphocytic meningitis
- Cerebellar ataxia
- Cranial nerve palsy
- Peripheral neuropathy.

9. Kidneys:

- Glomerulonephritis (commonly proliferative, may be mesangial, focal or diffuse, and membranous)
- Nephrotic syndrome
- Renal vein thrombosis.

10. Others—lymphadenopathy, infertility, abortion, menorrhagia.

Q. What are the features of **renal involvement** in SLE?

A. Renal involvement occurs in 1/3rd of SLE, of these 25% develop end stage renal failure within 10 years. Lupus nephritis is classified histologically by WHO.

Type	Histology	Clinical features
Type I	**Minimal** mesangial lupus nephritis (LN), normal on light microscopy	Asymptomatic
Type II	**Mesangial** proliferative LN with mesangial hypercellularity and matrix expansion	Mild renal disease
Type III	**Focal** LN (involving < 50% glomeruli) Subepithelial deposits seen	Hematuria and proteinuria
Type IV	**Diffuse** LN (involving ≥ 50% glomeruli) There are segmental and global lesions as well as active and chronic lesions. Subendothelial deposits are present	Progression to nephrotic syndrome, hypertension and renal insufficiency. It is the most common and most severe form of LN
Type V	**Membranous** LN, occurs in 10 to 20% patients. Can occur in combination with type III and IV	Heavy proteinuria (NS), hematuria, hypertension. Good prognosis
Type VI	Advanced **sclerosing** LN. It causes sclerosis of > 90% glomeruli	Progressive renal failure, severe form

Treatment of LN:

- Type I—no treatment
- Type II—benign. But sometimes, steroid may be needed

- Type III, IV and V—immunosuppressive therapy with steroid and cyclophosphamide or mycophenolate mofetil are used for induction. Then azathioprine and mycophenolate mofetil are used for maintenance
- Rituximab (anti CD-20) may be used in some patient
- Symptomatic treatment for hypertension and edema.

Note Remember the following:

- Focal glomerulonephritis respond well to treatment with prednisolone 40 to 60 mg/day.
- Diffuse and membranous lesions do not respond well to steroid only. Pulse therapy with methylprednisolone for 3 days followed by maintenance with prednisolone is necessary. Sometimes azathioprine 2 to 3 mg/kg body weight or cyclophosphamide 100 to 150 mg daily with prednisolone may be given.
- Pulse therapy—IV cyclophosphamide is more effective than pulse methylprednisolone alone. Also, combination therapy is sometimes more effective. Continuing IV treatment, quarterly for one year, after renal remission decreases the risk of renal flare.
- Prognosis is better in type I, II and V.

Q. How to **diagnose renal involvement** in SLE?

A. The patient may present with nephrotic syndrome or acute nephritic illness or renal failure. Renal involvement is diagnosed by:

1. Urine for routine microscopie examination (R/M/E):
- Proteinuria (+++), hematuria, and granular or RBC cast
- UTP (24 hours urinary total protein) > 0.5 g

2. Blood:
- Urea and creatinine (high)
- Creatinine clearance rate (CCR)—low.

3. Renal biopsy.

Q. What are the **diagnostic criteria** of SLE?

A. The diagnostic criteria are (11 criteria):

1. Malar rash (fixed erythema, flat or raised, sparing the nasolabial folds)
2. Discoid rash (erythematous raised patches with adherent keratotic scarring and follicular plugging)
3. Photosensitivity
4. Oral ulcer (oral or nasopharyngeal ulcer that may be painless)
5. Arthritis (non-erosive, involving two or more peripheral joints)
6. Serositis:
   - Pleuritis (pleuritic pain, rub or pleural effusion)
   - Pericarditis (pericardial rub, ECG evidence or pericardial effusion)
7. Renal involvement:
   - Persistent proteinuria > 0.5 g per day, or
   - Greater than 3+ (if total urinary protein is not performed), or
   - Cellular casts (red cell, granular or tubular).
8. Neurological disorder seizure or psychosis in the absence of offending drug or metabolic derangement (uremia, ketoacidosis and electrolyte imbalance).
9. Hematological disorders:
   - Hemolytic anemia or
   - Leukopenia (< 4,000/cmm in two or more occasions) or
   - Lymphopenia (< 1,000/cmm in two or more occasions) or

- Thrombocytopenia (< 100,000/cmm in two or more occasions), in the absence of offending drug.

10. Immunological disorders:
    - Anti-DNA antibody in abnormal titer or
    - Anti-Sm antibody (antibody to Sm nuclear antigen) or
    - Positive anti-phospholipid antibody
    - False-positive serological tests for syphilis (positive for at least 6 months and confirmed by treponema pallidum immobilization or fluorescent treponemal antibody absorption test).
11. **ANA** positive (in the absence of drugs causing lupus syndrome).

Note Remember the following

Presence of **four or more** criteria at a time or sequential appearance is diagnostic. Positive anti-double-stranded DNA and anti-Sm (Smith) antibodies are diagnostic of SLE.

Q. What is the **type of arthritis** in SLE?

A. Usually non-erosive and non-deforming. Rarely, deformity may occur similar to RA called Jaccoud's arthritis. Aseptic necrosis of head of femur may occur.

Q. What is the cause of **avascular necrosis** of head of femur in SLE?

A. It is because of

- Vasculitis in SLE
- Prolonged use of steroid therapy (actual cause of necrosis because of steroid is unknown. Probably steroid causes hypertrophy of lipocytes that compresses blood vessels, leading to ischemic necrosis of bone).

Q. What is the cause of **backache** in SLE?

A. Avascular necrosis (that is because of vasculitis and steroid therapy).

Q. What are the differential diagnoses of **butterfly rash**?

A. As follows:

- Systemic lupus erythematosus (SLE) or discoid lupus erythematosus (DLE)
- Dermatomyositis
- Mixed connective tissue disease (MCTD)
- Sarcoidosis
- Drug rash
- Acne rosacea (characterized by red patch with telangiectasia on the face with papules and pustules, that are absent in SLE)
- Lepromatous leprosy
- Post-kala-azar dermal leishmaniasis (PKDL).

Q. What are the **atypical features** of SLE?

A. As follows:

- Raynaud's phenomenon
- Chorea
- Repeated abortion
- Epilepsy or cerebrovascular accident (CVA) in young age
- Psychiatric disorder.

Q. What are the **types** of SLE?

A. As follows:

A. According to presence of **American Rheumatism Association (ARA) criteria:**

- Possible SLE—when 2 criteria are present
- Probable SLE—when 3 criteria are present
- Definite SLE—when 4 or more criteria are present
- Classic SLE—when many criteria are present.

B. According to the **severity:**

1. **Mild:**
   - Fever
   - Arthralgia or arthritis
   - Rash, headache
   - Mild pericarditis or mild pericardial effusion
   - Mild pleural effusion.
2. **Severe:**
   - Massive pleural effusion
   - Massive pericardial effusion
   - Renal involvement
   - CNS involvement
   - Acute vasculitis
   - Myocarditis
   - Lupus pneumonitis
   - Hemolytic anemia
   - Thrombocytopenic purpura.

Q. What is '**disseminated lupus erythematosus**' (DLE)?

A. It is a variant of SLE in which the disease is mainly limited to skin, characterized by photosensitivity, discoid rash, erythema, scaling, follicular plugging and telangiectasia. M:F = 1:2 (in SLE, the ratio is 1:9). SLE may occur in 5% cases (more in children). ANA is positive (30% cases), anti-double-stranded DNA is negative and complements are normal.

Treatment of DLE:

- Hydroxychloroquine—200 to 400 mg/day
- In severe cases, prednisolone
- Use of sunscreen and topical steroid may help.

Q. What is **SCLE (subacute cutaneous lupus erythematosus)?**

A. It consists of scaly red patch or circular, flat, red lesions (confused with psoriasis), highly photosensitive. Most patients have anti-Ro (SSA).

Q. What are the **drugs causing SLE?**

A. As follows:

- Hydralazine (slow acetylator)—the most common cause (90%)
- Procainamide (rapid acetylator)
- Anticonvulsant (carbamazepine and phenytoin)
- Phenothiazine
- Isoniazid (INH)
- Oral contraceptive pill
- ACE inhibitor

- Penicillamine
- Methyldopa
- Minocycline.

Features of drug induced SLE**:**
- Sex ratio—equal
- Renal and neurological involvements are absent. Lung involvement is common
- ANA is usually positive, but anti-ds DNA is negative
- Complements are normal
- Anti-histone antibody is positive in 95% cases (characteristic, but not specific)
- Drugs causing SLE-like syndrome usually do not aggravate primary SLE
- Clinical features and laboratory abnormalities revert to normal, when the offending drugs are withdrawn.

Treatment:
- Withdrawal of drugs
- Occasionally a short course of steroid is necessary.

Q. What is the relation of **pregnancy with SLE?**

A. Pregnancy is not contraindicated. Fertility is usually normal except in severe disease. Repeated abortion (due to the presence of anti-phospholipid antibody), still birth and intrauterine growth retardation may occur.

The disease should be in remission and pregnancy should be avoided if there is neurological, renal and cardiac abnormality. Relapse may occur in the first trimester and in puerperium.

If the mother has "**anti-Ro antibody"** (SSA), there may be congenital complete heart block of the baby, due to transplacental transfer of antibody. With anti Ro or anti La antibodies in mother, there is 2% risk of giving birth to a baby with neonatal lupus syndrome. This is characterized by skin rash, hepatitis and fetal heart block.

Treatment of SLE during pregnancy: Prednisolone should be continued (avoid dexamethasone and betamethasone that are broken by placental enzymes).

Q. What are the causes of **abdominal pain in SLE?**

A. As follows:
- Mesenteric vasculitis or perforation of gut
- Peptic ulcer as a complication of steroid
- Perisplenitis or splenic infarction
- Pancreatitis.

Q. How to **treat** SLE?

A. As follows:

1. General measures:
- Explanation and education regarding the nature of the disease
- Reassurance
- Psychological support
- Avoidance of UV light exposure, use of sun blocks
- Cardiovascular risk factors like hypertension and hyperlipidemia should be controlled. Smoking should be stopped.

2. Drug therapy:
- Mild cases—NSAID (if fever, arthralgia and headache)

- Chloroquine or hydroxychloroquine—effective in cutaneous lesion, arthritis, arthralgia and serositis without organ involvement
- Rash, synovitis or pleuropericarditis—short course steroid
- Severe and active disease—steroid should be given
- Acute life-threatening SLE affecting kidney, CNS or CVS, hemolytic anemia, thrombotic thrombocytopenia—high dose steroid and immunosuppressive drug. Pulse methylprednisolone (500 mg to 1 g IV) daily for 3 to 5 days. Cyclophosphamide (2 mg/kg IV) may be given 2 to 3 weekly on 6 to 8 occasions.
- In renal involvement—mycophenolate mofetil may be used instead of cyclophosphamide
- In thrombocytopenia not responding to immunosuppressive therapy, danazol may be used.

Steroid (prednisolone):

Indications:

- In mild disease, not responding to chloroquine and NSAID
- Severe and active disease with involvement of organ (heart, kidney, CNS and hematological abnormality).

Dose:

- Without major organ involvement—0.25 to 0.5 mg/kg/day
- Major organ involvement—1 to 1.5 mg/kg/day.

Dose schedule of steroid (one suggested regimen):

- Initially, full dose (45.0 to 60.0 mg daily) for 4 to 8 weeks, then-
- Reduce 10.0 mg weekly till 30.0 mg, then-
- 25.0 mg/day for 1 week, then-
- 20.0 mg/day for 1 week, then-
- 15.0 mg for 1 month, then-
- Reduce 2.5 mg every 2 weekly as follows:
  - First day 15.0 mg, second day 12.5 mg for 2 weeks, then-
  - First day 15.0 mg, second day 10.0 mg for 2 weeks, and so on.
  - This is continued until 2nd day regimen is completed, then-
- 15.0 mg on alternate day (continue and follow-up).

When the disease activity (both clinically and biochemically) disappears, steroid should be reduced slowly over months and can be withdrawn (may be needed to continue for 2 to 3 years. For lupus nephritis, treatment is usually given for 5 years).

Methylprednisolone:

Indication: Severe SLE, when there is carditis, renal and cerebral involvement, poor general condition.

Dose: 500 mg to 1gm mixed with 200 mL 5% DA IV daily for 3 to 5 days, followed by prednisolone 1mg/kg for 6 to 10 weeks, then gradual tapering.

Cyclophosphamide:

Indications:

- Renal lupus (classes III, IV and V)
- Severe renal disease as evidenced by (UTP > 1 g, raised serum creatinine and decreased creatinine clearance)
- CNS involvement.

Dose:

- 0.5 to 1 g/m^2 of body surface area. It is given monthly as a pulse therapy IV with 500 mL fluid (every month for six cycles, then every 3 months for another six cycles or till the disease is inactive for 1 to 2 years). Then hydroxychloroquine or azathioprine can be started.
- Alternately, cyclophosphamide 250 mg/m^2 of body surface may be given every 15 days for 12 doses, followed by prednisolone as maintenance therapy.
- Oral cyclophosphamide can be given.
- After 12 weeks of cyclophosphamide, oral azathioprine (2 to 2.5 mg/kg daily) may be given.
- Advantages of azathioprine—no gonadal toxicity and no adverse effect on pregnancy.
- Cyclophosphamide can cause hemorrhagic cystitis, gonadal toxicity, amenorrhea, sterility, premature menopause and sometimes, leukemia. Moreover, it can not be continued in pregnancy.
- Cyclophosphamide is usually given with high dose prednisolone.

(Periodic blood count should be done initially 2 weekly, then monthly.)

Q. What is the **mechanism of hemorrhagic cystitis?** How to **prevent** this?

A. Cyclophosphamide can cause hemorrhagic cystitis (more by oral route). It is due to production of **acrolein**, a metabolite from cyclophosphamide that is highly toxic to the mucosa of the urinary bladder.

This can be prevented by:

- Plenty of fluid (3 to 4 L)
- Using mesna (0, 4 and 8 hours of therapy)
- Advise the patient to micturate frequently.

Prognosis in SLE:

- 10-year survival rate is 90%, but this is lower if vital organs are involved (heart, kidney, lung, CNS).
- Mortality shows bimodal pattern. In early age, death is usually because of infection (mostly opportunistic), renal or cerebral disease. In later age, accelerated atherosclerosis is common, incidence of myocardial infarction is 5 times more than in general population (so, risk factor for atherosclerosis should be avoided, such as avoid smoking, control hypertension, obesity, hyperlipidemia, etc.).
- In the long-term, some patients may develop cancers, especially lymphoma.
- Rarely, there may be deforming arthritis, chronic progressive destruction of joints and osteoarthrosis.

Q. What is **anti-phospholipid syndrome**?

A. Anti-phospholipid syndrome is characterized by the presence of anti-phospholipid antibody, associated with recurrent arterial or venous thrombosis, recurrent fetal loss or thrombocytopenia. Some patients with anti-phospholipid antibody may not get anti-phospholipid syndrome. It is positive in SLE and may be found in many other cases. But may be positive without any cause, called primary anti-phospholipid syndrome.

Two types of anti-phospholipid antibody:

- Anti-cardiolipin antibody—may be IgG or IgM. IgG is more pathogenic
- Lupus anticoagulant—it interferes with phospholipid dependent coagulation tests.

In some patients, only one of these is positive and in others, both are positive.

Presence of anti-phospholipid antibody is associated with:

- Thrombosis, venous or arterial.17% of stroke < 45 years of age is thought to be due to anti-phospholipid antibody
- Recurrent abortion or intrauterine growth retardation
- Hematological—thrombocytopenia and autoimmune hemolytic anemia
- Neurological—epilepsy, TIA, stroke, migraine and chorea
- Heart—sterile endocarditis (Libman-Sacks)
- Renal involvement with proteinuria and lupus nephritis (membranous)
- Skin-ulceration, livedo reticularis, gangrene and necrosis of digit.

It is of 2 types:

1. Primary—it causes thromboembolism without features of SLE.
2. Secondary—causes are:
   - Rheumatological—SLE, DLE, RA, systemic sclerosis, Sjögren's syndrome, psoriatic arthropathy, dermatomyositis
   - Vasculitis—Behcet's syndrome, temporal arteritis, Takayasu's arteritis
   - Malignancy—solid tumors, such as bronchial carcinoma, hypernephroma, prostatic carcinoma, thymoma, esophagial carcinoma
   - Hematological disease—leukemia, lymphoma, myelofibrosis, polycythemia, myeloma, monoclonal gammopathy
   - Infections—HIV, infectious mononucleosis, rubella, parvovirus, hepatitis, TB, leprosy, infective endocarditis, klebsiella, syphilis
   - Drug induced—procainamide, phenothiazine
   - Miscellaneous—diabetes mellitus, dialysis patient.

In < 1% cases of antiphospholipid syndrome, a severe type called catastrophic antiphospholipid syndrome may occur. In such case, there may be diffuse thrombosis, thrombotic microangiopathy and multiorgan failure. It is treated with intravenous heparin, high dose steroid and intravenous immune globulin and plasmapheresis.

Investigations:

1. Serum anti-phospholipid antibody (anti-cardiolipin and lupus anticoagulant)
2. Indirect tests for anti-phospholipid antibody (anti coagulant):
   - Thrombocytopenia
   - False positive VDRL
   - Prolonged prothrombin time
   - Prolonged APTT that is not corrected by addition of normal plasma.

Treatment anti-phospholipid syndrome:

- With thrombosis—warfarin should be continued for life long.
- Without history of thrombosis, but with antiphospholipid antibody only, aspirin or clopidogrel may be given. Rarely, warfarin may be needed.
- In pregnancy—low dose aspirin and subcutaneous heparin should be started early in gestation. This reduces the chance of miscarriage, but pre-eclampsia and poor fetal growth remains common.

RHEUMATOID ARTHRITIS

CHIEF COMPLAINTS

- Pain and swelling in multiple joints of both hands and feet for … months
- Fever, anorexia and weight loss for … months.

HISTORY

History of present illness: According to the statement of the patient, she was alright … months back. Since then, she has been suffering from pain and swelling involving small joints of both hands and feet. Initially pain was mild, but gradually it has become severe and incapacitating. The pain is associated with morning stiffness that persists for about two hours and is relieved by activity or exercise. She also complains of continued low grade fever, substantial weight loss, malaise and anorexia for the last … months. There is no history of mouth ulcer, skin rash, photosensitivity, eye problems, breathlessness, cough, chest pain or alopecia. Her bowel and bladder habits are normal.

History of past illness: Mention according to the patient's statement.

Family history: All the family members are in good health. No such illness in the family.

Personal history: Mention according to the patient's statement.

Drug and treatment history: He used to take painkiller, such as indomethacin, diclofenac, but no disease modifying drugs.

Menstrual history: Mention according to the patient's statement.

Socioeconomic history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient looks ill and anxious
- Moderately anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- There is no nail fold infarct or skin rash or vasculitis
- Pulse—88/min
- BP—110/80 mm Hg
- Temperature—99^0 F.

SYSTEMIC EXAMINATION

Musculoskeletal System

Examination of hands:

1. **Inspection:**
   - Wrist joints are swollen. PIP joints of both hands are spindle shaped. There is swan neck deformity in right little and ring fingers, Z deformity in right thumb and ulnar deviation of the right hand. There is mild flexion deformity of fingers on right hand as evident by prayer sign.
   - There is wasting of thenar and hypothenar muscles with dorsal guttering in both hands. There is no atrophy, ulcer, infarction, gangrene or rash.

- Movement is restricted in both wrists and fingers of both hands with slightly impaired functional activity.

2. **Palpation:**
   - All the joints of both hands are tender
   - Synovial thickening is present in both wrists
   - There is a rheumatoid nodule in the extensor surface of the right forearm.

Examination of feet:

- All the metatarsophalangeal joints and interphalangeal joints are swollen and deformed in both feet
- Lateral deviation with dorsal subluxation of toes
- Plantar subluxation of the metatarsal head
- Hallus valgus deformity
- Feet are flat with plantar erythema.

Examination of other joints:

- Both the knee joints are swollen and tender. There is no Baker cyst or popliteal cyst
- Elbow joints—swollen, tender with some flexion deformity.

Examination of eyes:

- No redness, no nodule.

Examination of respiratory system:

- Normal (No bilateral basal crepitations).

Examination of CVS:

- No abnormality detected.

Examination of the nervous system:

- No evidence of peripheral neuropathy, carpal tunnel or tarsal tunnel syndrome.

Examination of abdomen:

- There is no splenomegaly (to exclude Felty's syndrome).

SALIENT FEATURES

Mrs …, 55 years, housewife, normotensive, nondiabetic, hailing from …, presented with pain and swelling involving small joints of both hands and feet for ... months. Initially pain was mild, but gradually it has become severe and incapacitating. The pain is associated with morning stiffness that persists for about two hours and is relieved by activity or exercise. She also complains of continued low grade fever, substantial weight loss, malaise and anorexia for the last … months. There is no history of mouth ulcer, skin rash, photosensitivity, eye problems, breathlessness, cough, chest pain or alopecia. Her bowel and bladder habits are normal. All the family members are in good health. No such illness in the family. She used to take painkiller, such as indomethacin, diclofenac, but no disease modifying drugs.

On examination, on general examination (mention as above).

On systemic examination (mention as above. Always never forget to mention the extra-articular features).

My diagnosis is rheumatoid arthritis.

Q. What is your **differential diagnosis?**

A. Systemic lupus erythematosus **(**SLE), mixed connective tissue disease (MCTD), and seronegative arthritis (SNA) (However, if the history and physical findings are typical of Rheumatoid arthritis, no differential diagnosis).

Q. **Could it be** seronegative arthritis or ankylosing spondylitis?

A. No, as is seronegative arthritis there is usually asymmetrical involvement of the bigger joints. But in this case, there is bilateral symmetrical involvement of small peripheral joints associated with morning stiffness that persists more than 1 hour.

Q. Which joint is **spared** in RA?

A. Distal interphalangeal joint (may be involved in secondary osteoarthrosis).

RELATED QUESTIONS AND ANSWERS

Q. **What** is RA?

A. It is 13
r menopause, sex ratio is almost equal.

Q. What are the mechanisms of **wasting of muscles** in RA?

A. Multiple factors are responsible—disuse, vasculitis, polyneuropathy, mononeuritis multiplex and entrapment neuropathy.

Q. What is **boutonniere deformity**? What is the **mechanism?**

A. Fixed flexion of PIP joint and extension of DIP joint. Because of chronic synovitis of PIP joint, there is rupture of central slip of extensor tendon, allowing to protrude the joint between two lateral slips of extensor tendon.

Q. Why it is called **boutonniere** or **button-hole?**

A. Because of rupture of central slip of extensor tendon, it looks like the gap of button hole.

Q. What is **swan neck deformity**? What are the **mechanisms?**

A. Fixed flexion of DIP joint and extension of PIP joint (reverse of boutonniere).
Mechanism—because of chronic synovitis:

- Rupture or stretching of extensor tendon on dorsum of DIP joint
- Secondary to stretching of volar plate at PIP joint
- Shortening of intrinsic muscles of hands that exert tension of dorsal tendon sheath leading to hyperextension of PIP joint.

Q. Why **Z-deformity** of thumb?

A. Because of chronic synovitis, there is hyperextension of IP joints and fixed flexion and subluxation of metacarpophalangeal (MCP) joints of thumb.

Q. Why **radial deviation?**

A. Weakness of extensor carpi ulnaris leads to radial deviation at wrist as the carpal bone rotates.

Q. Why **ulnar deviation?**

A. It occurs in response to radial deviation to keep the tendons to the phalanges in normal line to the radius.

Q. What is rheumatoid nodule? Where is it found?

A. These are painless, firm, subcutaneous nodule, invariably associated with positive rheumatoid factor. It is present in 20 to 30% cases of rheumatoid arthritis.

Sites: Pressure points, such as elbow, extensor surface of forearm and hands (fingers), scapula, scalp, sacrum, shin, Achilles tendon, toes, sclera, pleura, lungs and pericardium.

Significance of rheumatoid nodule:
- It is one of the diagnostic criteria
- Associated with high titer of rheumatoid factor (positive RA test)
- Associated with active and aggressive RA
- A bad prognostic sign.

Histologically 3 zones:
- Central zone of necrotic material including collagen fibril, noncollagen filament and cellular debris
- Mid zone of palisading macrophages
- Outer zone of granulation tissue.

Nodules may ulcerate and become infected. Treatment with methotrexate may increase the number of rheumatoid nodule in some patients.

Nodules resolve when the disease is under control. If it causes problem, it may be removed surgically or by local injection of corticosteroid.

Note Remember the following:

Rheumatoid nodules may be confused with tophi of gout, xanthomata, olecranon bursa in elbow, sarcoid nodule or neurofibroma.

Q. What is Baker's cyst?

A. Cyst on the back of knee joint, communicates with the joints but fluid is prevented from returning to the joint by a valve-like mechanism. May rupture during knee flexion and fluid enters into the calf. After rupture, severe pain, swelling and tenderness in the calf. It is confused with DVT.

Diagnosis: USG of knee joint. Sometimes, CT scan or MRI and arthrogram may be done.

Treatment after rupture of Baker's cyst:
- Relief of pain by NSAID
- Elevation of the limb, rest and observation
- Antibiotic, if necessary
- Intra-articular injection—methylprednisolone or triamcinolone may be given
- Surgical toileting and removal of cyst, if necessary.

Q. What are the causes of Baker's cyst?

A. Commonly in RA. Also in osteoarthrosis and rarely congenital.

Q. What are the diagnostic criteria of rheumatoid arthritis?

A. ARA (American Rheumatism Association criteria):
1. Morning stiffness (> 1 hour)
2. Arthritis of three or more joint areas
3. Arthritis of hand joints and wrist
4. Symmetrical arthritis
5. Rheumatoid nodule

6. Positive RA factor
7. Typical radiological changes (erosion or periarticular osteopenia).

The duration should be 6 weeks or more. There are 14 joint areas in the body for diagnosis of RA. They are—elbow, wrist, PIP, MCP, knee, ankle, MTP of both sides ($7 \times 2 = 14$).

Note Remember the following:

When four or more criteria are present, there is 93% sensitivity and 90% specificity.

Q. What are the **extra-articular** manifestations of RA?

A. As follows:

1. Eye:
- Episcleritis
- Scleritis
- Scleromalacia
- Scleromalacia perforans
- Keratoconjunctivitis sicca.

2. Respiratory:
- Pleurisy
- Pleural effusion (may be bilateral)
- Fibrosing alveolitis
- Nodules in the lungs (in Caplan's syndrome)
- Bronchiolitis.

3. Cardiac:
- Pericarditis (30%)
- Pericardial effusion (rare)
- Chronic constrictive pericarditis (rare)
- Rarely myocarditis, endocarditis, conduction defect, heart block, dysrhythmia, cardiomyopathy, aortic regurgitation, coronary vasculitis, coronary artery occlusion and granulomatous aortitis.

4. Vasculitis:
- Digital arteritis and nail fold infarct
- Ulcers
- Raynaud's phenomenon
- Visceral arteritis
- Mononeuritis multiplex
- Pyoderma gangrenosum.

5. Neurological:
- Entrapment neuropathy (compression of nerves by hypertrophic synovium), commonly carpal tunnel syndrome (compression of median nerve) and tarsal tunnel syndrome (compression of posterior tibial nerve)
- Peripheral neuropathy
- Mononeuritis multiplex
- Cervical cord compression (due to atlanto-axial subluxation)
- Progressive cervical myelopathy.

6. Hematological:
- Anemia (usually normocytic normochromic, occasionally macrocytic because of folate deficiency or associated with pernicious anemia and microcytic hypochromic because of bleeding from NSAID)

- Thrombocytosis
- Eosinophilia
- Pancytopenia (because of hypersplenism in Felty's syndrome).

7. Musculoskeletal:
- Muscle wasting
- Tenosynovitis
- Bursitis
- Osteoporosis.

8. Others:
- Lymphadenopathy
- Splenomegaly
- Nodules causing sinus or fistula
- General features (fatigue, fever, weakness, loss of weight, susceptibility to infection)
- Amyloidosis.

Note Remember the following:

Persistent inflammatory process in rheumatoid arthritis may cause large B cell lymphoma.

Q. What is **rheumatoid factor?**

A. Rheumatoid factor is an antibody, directed against Fc portion of IgG. It may be IgM or IgG type. Rheumatoid factor is positive in 75% cases, but 100% positive in RA with extra-articular manifestations. It is detected by latex slide test (RA test is more sensitive, but less specific, and is used for screening) and Rose Waaler test (RW test, the sheep cell agglutination test, is less sensitive, but more specific). Other causes of positive rheumatoid factor are:
- Collagen diseases—Sjögren's syndrome (90%), SLE (30%), systemic sclerosis, dermatomyositis, fibrosing alveolitis and mixed essential cryoglobulinemia
- Infections—infectious mononucleosis, infective endocarditis, tuberculosis, leprosy, kala-azar, hepatitis B, syphilis, malaria, filariasis and schistosomiasis
- Liver disease—PBC (50%)
- Sarcoidosis
- Temporarily after vaccination and blood transfusion
- Over 65 years (20% in normal population).

High titer of rheumatoid factor indicates:
- Severe erosive disease
- More extra-articular manifestations
- Poor prognosis
- Associated with rheumatoid nodule, vasculitis and Felty's syndrome.

Q. What are the **presentations** of RA?

A. As follows:
- Chronic persistent—common (65 to 70%)
- Remitting type (5 to 10%)
- Rapidly progressive (5%)
- Palindromic type (5%).

Pattern of onset:
- Monoarticular (20%)

- Oligoarticular (45%)
- Polyarticular (35%).

Mode of onset:
- Insidious (70%)
- Acute (15%)
- Systemic (10%)
- Palindromic (5%).

Site of onset:
- Small joints (32%)
- Medium size joints (16%)
- Large joints (29%)
- Combined (26%).

Q. What is **malignant** RA?

A. Severe and progressive RA associated with severe extra-articular manifestations, systemic features and vasculitis.

Q. What is **palindromic** RA?

A. Recurrent acute episode of monoarthritis lasting 24 to 48 hours. Knee and finger joints are most commonly affected, but any peripheral joint may be involved. Fever may occur, but no other systemic features. It may be confused with acute gouty arthritis and atypical onset of rheumatoid arthritis. There may be many attacks without any permanent articular damage. However, one-third to half cases may develop typical RA. This can be treated with NSAID during pain. Hydroxychloroquine may be used in preventing recurrent attack.

Q. What is **Caplan's syndrome**?

A. Rheumatoid lung nodules with pneumoconiosis is called Caplan's syndrome. Common in coal-workers pneumoconiosis, may occur in any pneumoconiosis. Nodules are rounded, 0.5 to 2.5 cm, present at periphery of the lung. These may rupture causing pneumothorax or may cavitate and cause hemoptysis. It may be confused with tuberculosis or neoplasm.

Q. What is **Felty's syndrome**?

A. Rheumatoid arthritis with splenomegaly and neutropenia is called Felty's syndrome. There may be hypersplenism (anemia, leukopenia and thrombocytopenia). It occurs in long standing, seropositive, deforming, but inactive arthritis, in < 1% of the cases. Female is more affected than male, age 50 to 70 years. Leg ulcers or sepsis are complications due to neutropenia. Splenectomy may be necessary for hypersplenism. It is associated with high titer of rheumatoid factor, subcutaneous nodules and other manifestations of systemic rheumatoid disease.

Q. What are the **mechanisms of anemia** in rheumatoid arthritis?

A. Multiple factors are responsible:
- Anemia of chronic disorder
- Megaloblastic anemia (because of either folate deficiency or vitamin B_{12} deficiency, if associated with pernicious anemia)
- Hypersplenism (in Felty's syndrome)
- Hemolytic anemia (Coombs' test may be positive)
- GIT bleeding (due to NSAID or vasculitis causing iron deficiency anemia)
- Marrow suppression (gold and penicillamine—though less or no use now a days).

Q. What are the **investigations** done in RA?

A. As follows:

- FBC (ESR is high, pancytopenia may occur in Felty's syndrome)
- RA test and RW test
- Anti-CCP antibody (cyclic citrullinated peptide)
- X-ray of hands and other involved joints, chest X-ray to see fibrosis, pleural effusion, nodule, cardiomegaly
- Others—CRP (high) and urine analysis (proteinuria, may occur in amyloidosis).

Q. What are the **ARA criteria for disease activity** in RA?

A. As follows:

1. Number of tender joints
2. Number of swollen joints
3. Patient's global assessment
4. Physician global assessment
5. VAS—(visual analog scale for pain)
6. Duration of morning stiffness
7. ESR or CRP.
8. Functional assessment health status (HAQ—health assessment questionnaire).

Q. What precaution is necessary before **general anesthesia or upper GI endoscopy**?

A. X-ray of the cervical spine should be taken to rule out atlanto-axial subluxation. (Otherwise during anesthesia, cervical cord compression may lead to sudden death).

Q. If the patient develops **nephrotic syndrome** (or proteinuria in urine examination), what is the likely cause?

A. Renal amyloidosis.

Q. What is **anti-CCP antibody**? What is its **significance?**

A. It is the antibody to cyclic citrullinated peptide (CCP). It binds to peptides in which the amino acid arginine is converted to citrulline by peptidyl arginine deaminase, an enzyme abundant in inflamed synovium.

Anti-CCP antibody is highly specific in RA (95%), present in 70% patients with rheumatoid arthritis. Unlike rheumatoid factor, it is not positive in other autoimmune diseases. It is helpful for early diagnosis and is also a predictor of an aggressive disease. In patient with undifferentiated arthritis, anti-CCP antibody is helpful for early diagnosis of RA. It may be detected in asymptomatic patient several years before the development of RA.

Q. How to **treat** RA?

A. As follows:

- Relief of symptoms by rest and NSAID. Also intra-articular injection, splinting, hydrotherapy, etc. may relieve symptoms.
- Suppression of activity and progression of disease by disease modifying anti-rheumatic drug (DMARD).
- Other measures—physiotherapy, orthopedic measures. Synovectomy of the wrist or finger tendon sheaths of the hands may be required for pain relief or to prevent tendon rupture when medical interventions have failed. Osteotomy, arthrodesis or arthroplasty may be needed later.
- Patient's education is important.

Q. What are the **surgical** treatments in RA?

A. As follows:

- Synovectomy of wrist or finger tendon sheath (for pain relief or tendon rupture)
- In advanced or severe cases—arthrodesis, arthroplasty and osteotomy may be done in selected cases.

Q. What are the **criteria for remission** of RA?

A. As follows:

- No joint pain
- No fatigue
- No joint tenderness
- Morning stiffness less than 15 minutes
- No soft tissue swelling
- ESR less than 30 mm in 1st hour.

At least 5 criteria must be present for at least 2 consecutive months.

Q. What are the **bad or poor** prognostic factors of RA?

A. As follows:

1. Clinical:
   - Insidious rather than explosive onset
   - Early development of rheumatoid nodule
   - Extra-articular manifestations
   - Severe functional impairment
   - One year active disease without remission
   - Increasing number of peripheral joints involvement
   - Level of disability at the onset
   - Female sex.
2. Blood tests:
   - High titers of anti-CCP antibodies and RA test
   - High CRP
   - Normochromic normocytic anemia.
3. X-rays:
   - Early erosive damage (Note: Ultrasound and MRI can show cartilage and bone damage prior to conventional X-rays).

Q. What **DMARDs** are used?

A. As follows:

- First choices are sulfasalazine and methotrexate.
- Other drugs—chloroquine, hydroxychloroquine, leflunomide, azathioprine, and cyclosporine (gold and penicillamine are not used any more).
- Anti-TNF alpha and IL-1, also rituximab are more effective than other DMARD in preventing joint erosions. If disease activity persists despite an adequate trial of two DMARDs, anti-TNF therapy should be considered.

The DMARD should be started from the beginning, may take 4 to 12 weeks for response. If no effect in 6 to 12 weeks, combination with methotrexate and sulfasalazine may be given. Prednisolone 7.5 to 10 mg may be added with DMARD to give symptomatic relief.

Brief Note About DMARDs

Sulfasalazine:

1. When taken by mouth, it is broken to sulfapyridine and 5-aminosalicylic acid (ASA). Sulfapyridine is effective in RA (ASA is effective in inflammatory bowel disease). It acts probably by inhibiting cyclo-oxygenase and other enzymes responsible for synthesis of prostaglandin.
2. Dose—start with low dose, increase the dose every weekly.
   - Initially, 250 mg (½ tablet) BID for 1 week,
   - Then 500 mg (1 tablet) BID for 1 week,
   - Then 1,000 mg (2 tablets) BID to be continued (maximum dose 2 to 3 g daily).
3. Side effects—GIT upset (anorexia, nausea, vomiting, diarrhea), skin rash, Stevens Johnson syndrome, reversible sterility in males, blood dyscrasias (agranulocytosis, megaloblastic anemia and hemolytic anemia).
4. Periodic check up—FBC, liver function test (SGPT) and renal function tests (creatinine), every 1 to 3 months.

Methotrexate:

- Very effective DMARD. May take 4 to 6 weeks to act.
- Dose—7.5 to 10 mg, in a fixed day weekly (up to 25 mg). Folic acid 5 mg/day should be given on the next day (folinic acid is more preferable).
- Side effects—Anorexia, nausea, vomiting (prevented by using anti-emetic before starting the drug). Rarely, may cause bone marrow depression. Prolong use may cause hepatic fibrosis and DPLD.
- Periodic check up—CBC, liver function tests (SGPT) and renal function test (creatinine) should be done.
- Mechanism of action—competitively inhibits dihydrofolate reductase that interferes with DNA synthesis and cell division.

Chloroquine:

- It is a weak with slow DMARD effect.
- Dose—250 mg daily as a single dose.
- Side effects—Anorexia, nausea, vomiting, skin rash. Prolonged use may cause neuromyopathy and ocular toxicity. In eye, corneal microdeposit (reversible after drug withdrawal), retinopathy (may cause blindness), bull's eye macula and optic neuritis.
- Periodic examination of eye is essential. To reduce ocular toxicity, the drug can be given for 10 months in a year.

Hydroxychloroquine:

- Dose—200 to 400 mg daily
- Used alone in mild disease or as an adjuvant with other DMARD
- Retinopathy is the serious complication, but this is rare before 6 years of treatment.

Leflunomide:

- It can be used if methotrexate fails to respond. Also can be used together with methotrexate.
- Dose—100 mg daily for 3 days, then 10 to 20 mg daily.
- Side effects—Skin rash, diarrhea, reversible alopecia, hepatotoxicity, carcinogenic and teratogenic. It needs a washout of 2 years before conception (3 months in man and 2 years in female), so avoid in women who want to be pregnant.
- Periodic blood checkup is mandatory.

Biological agents:

These agents block specific immune factors responsible for RA. Drugs are—anti-TNF α and IL-1 receptor antagonist. These are highly expensive, used only when there is failure of 2 DMARDs.

Anti-TNF α:

1. It is more effective, rapid onset of action, greater clinical efficacy and sustained benefit than standard DMARD.
2. Anti-TNF drugs are:
   - Infliximab (given in infusion every 1 to 2 months)
   - Etanercept (given SC every 2 weeks)
   - Adalimumab (given SC every 2 weeks).
3. Common side effects: Hypersensitivity reaction, headache, hypotension. Reactivation of latent tuberculosis may occur. Sometimes lymphoma may occur.

Anti-interleukin (IL-1) receptor antagonist:

- Anakinra may be used in RA when anti-TNF α is unsuccessful (less effective than anti-TNF). It is used in combination with methotrexate.

Anti-interleukin 6 (IL-6) receptor:

- Tocilizumab: It is a humanized monoclonal antibody against IL-6 receptor. It acts similar to those of TNF blockade. It is used for treatment of moderate to severe active rheumatoid arthritis in adult patient, alone or in combination with methotrexate and/or other DMARDs. Dose—8 mg/kg as IV infusion, once in every 4 weeks.

Rituximab:

- It is an antibody directed against the CD-20 receptor, expressed on B lymphocytes.
- It produces significant improvement in RA positive patients. May be used alone or in combination with steroid or methotrexate.
- It is given by 2 IV infusions (1 g each) 2 weeks apart.

Q. What is **Sjögren's syndrome**? How will you **confirm** it?

A. It is an autoimmune disorder characterized by dryness of eye (keratoconjunctivitis sicca) and dryness of mouth (xerostomia) with nonerosive arthritis. Fibrosis and atrophy of the salivary glands occur. There is infiltration of lymphocytes and plasma cells in lacrimal and salivary glands. It is of 2 types:

- Primary—not associated with collagen disease (sicca syndrome)
- Secondary—associated with collagen disease (commonly RA).

Presentation of primary Sjogren's syndrome—common in females, F:M = 9:1, 40 to 50 years.

- Dryness of mouth and eyes
- Arthralgia and non-progressive arthritis
- Raynaud's phenomenon
- Dysphagia
- In lung—pulmonary diffusion defect and fibrosis
- Renal (renal tubular acidosis, nephrogenic diabetes insipidus)
- Vasculitis
- Others (fever, weakness, lymphadenopathy and neuropathy, fit, depression)
- Lymphoma—increased incidence of non-Hodgkin's B cell lymphoma. (It is associated with 40-fold risk).

- May be associated with other autoimmune disease, such as thyroid disease, myasthenia gravis, PBC, autoimmune hepatitis.

Investigations:

1. CBC (high ESR)
2. Schirmer test (a strip of filter paper is placed inside of lower eyelid. In normal people, at least 6 mm is wet in 5 minutes. In Sjögren's syndrome < 5 mm)
3. Biopsy of lip or salivary gland (lymphocytic and plasma cell infiltration)
4. Rose Bengal staining of eyes shows punctate or filamentary keratitis
5. Antibody test:
   - RA test (positive in 90%)
   - ANA (positive in 60 to 70%)
   - Anti-Ro (SS-A, positive in 70%. It can cross placenta causing congenital complete heart block)
   - Anti-La (SS-B).

Treatment:

- Artificial tear (hypromellose), contact lens, oral hygiene, artificial saliva, oral gel and chewing gum
- Stimulation of saliva flow by sugar free chewing gum or lozenges may be helpful
- Oral candidiasis should be promptly treated
- Vaginal dryness is treated with lubricants, such as K-Y jelly
- Hydroxychloroquine (2 to 3 mg/kg daily, may improve the flow of tear)
- Treat the primary cause
- Extraglandular and MSK manifestations may respond to steroid. Immunosuppressive drugs can be added.

Q. What are the **differences** between rheumatic fever and RA?

A. As follows:

Points	Rheumatic fever	RA
1. Age	5 to 15 years	20 to 40 years
2. Cause	Sequelae of immune response to *Streptococcus* β-hemolyticus sore throat	Autoimmune
3. Joints	Large	Peripheral small joints
4. Type of arthritis	Fleeting	Bilateral, symmetrical
5. Diagnosed by	Two major or one major and two minor criteria plus signs of previous *Streptococcus* infection	Four of seven criteria
6. Morning stiffness	Absent	Present
7. RA test	Negative	Positive
8. SC nodule	Present	Rheumatoid nodule
9. Erythema marginatum	Present	Absent
10. Joint deformity	Absent	Present
11. Cardiac involvement	Common	Less

Contd...

Contd...

12. Chronic constrictive pericarditis	Never	May cause
13. Chorea	May be present	Absent
14. Treatment	Prophylactic penicillin	DMARD
15. Sequelae	Rheumatic valvular lesion. It licks the joints, kills the heart.	Not so

DERMATOMYOSITIS

CHIEF COMPLAINTS

- Weakness and generalized muscular pain for … months
- Skin rash for … months
- Joint pain involving multiple joints for … months.

HISTORY

History of present illness: According to the statement of the patient, she was reasonably well … months back. Since then, she has been complaining of weakness, along with generalized muscle pain. Weakness is more marked during standing up from sitting position and raising both arms above head, especially while combing her hair. There is no diurnal variation of weakness. For last … months, she noticed reddish, scaly, non-itching skin rashes over her face, trunk, leg and hands that do not increase on exposure to sunlight. She also experiences joint pain involving the ankle, knee, wrist and small hand joints. Pain is aggravated by activity, slightly relieved by rest, but is not associated joint swelling or morning stiffness. She gives no history of fever, oral ulcer or respiratory symptoms. Her bowel and bladder habits are normal.

History of past illness: Mention according to the patient's statement.

Family history: No such illness in the family.

Personal history: Mention according to the patient's statement.

Drug and treatment history: Mention according to the patient's statement.

Menstrual history: Mention according to the patient's statement.

Socioeconomic history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient looks ill and anxious
- Face is puffy with periorbital edema and heliotrope rash over both upper eyelids
- Skin shows maculopapular, scaly, erythematous rash on the cheeks in a butterfly distribution, on forehead, dorsum of hands, upper arms, shoulders and on chest
- Telangiectasia present on face and hands
- Mildly anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- Pulse—84/min
- BP—120/70 mm Hg
- Temperature—98.6^0 F.

Note Remember the following:

Erythematous rash may be present on the neck and upper chest (in the shape of V—called **V** sign), or on the shoulders (Shawl sign).

SYSTEMIC EXAMINATION

Musculoskeletal System

1. **Hands:**
   - Maculopapular, scaly, erythematous rash on the dorsum of the hands. There are rashes with flat topped macules over the knuckles (Gottron's sign). Finger shows periungual erythema, ragged cuticles and hemorrhage.
   - Telangiectasia (dilated nailfold capillary) seen.
2. **Joints:** Swollen, tender with contracture deformity
3. **Muscles:**
   - Proximal myopathy is present both in the upper and lower limbs
   - Muscles are tender.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mrs …, 45 years, housewife, normotensive, nondiabetic, nonsmoker, hailing from …, presented with weakness and generalized muscle pain for … months. Weakness is more marked during standing up from sitting position and raising both arms above head, especially while combing her hair. There is no diurnal variation of weakness. For last … months, she noticed reddish, scaly, non-itching skin rashes over her face, trunk, leg and hands that do not increase on exposure to sunlight. She also experiences joint pain involving the ankle, knee, wrist and small hand joints. Pain is aggravated by activity, slightly relieved by rest, but is not associated joint swelling or morning stiffness. She gives no history of fever, oral ulcer, respiratory symptoms. Her bowel and bladder habits are normal. No such illness in the family. She was treated with painkillers and vitamins by local physicians.

On examination, general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is dermatomyositis.

Q. What are the **differences** of skin rash in dermatomyositis and SLE?

A. Rash in dermatomyositis usually involves knuckles, spares the phalanges. In SLE, it involves the phalanges, spares the knuckles.

Q. What are the **differential diagnoses**?

A. As follows:

- Systemic lupus erythematosus
- Mixed connective tissue disease (MCTD)
- Systemic sclerosis
- Sarcoidosis
- Polymyalgia rheumatica.

Q. Why not this is **polymyalgia rheumatica?**

A. Usually in polymyalgia rheumatica, there is no skin rash. About 30 to 50% cases are associated with temporal arteritis. CPK and other enzymes are typically normal that are high in dermatomyositis.

Q. What **investigations** should be done in dermatomyositis?

A. As follows:

1. FBC (ESR is high, but may be normal even in active disease)

2. Muscle enzymes:
   - Creatine phosphokinase (CPK) is very high (the most sensitive test)
   - Other enzymes—serum aldolase, SGOT, SGPT and LDH (may be high)
3. Electromyography—abnormal almost in every case, normal in 10%
4. Muscle biopsy shows the following findings:
   - Necrosis, swelling, vacuolation, disruption and fragmentation of muscles
   - Infiltration of lymphocyte, plasma cells, eosinophils and macrophages
   - Fibrosis
   - Perivascular inflammatory cells infiltration and thickening of vessel wall
5. Other tests:
   - To exclude malignancy (chest X-ray, USG, CT scan, MRI, PET scan, mammogram, gastrointestinal tract imaging)
   - Other X-rays (limbs or hands) to see soft tissue calcification. It is common in childhood dermatomyositis
   - RA test and ANF (positive in 50% cases)
   - Anti-Jo-1 antibody is more specific. Positive in 30% cases of dermatomyositis and 50% cases of polymyositis (if anti-Jo-1 antibody is present, respiratory muscles involvement may occur)
   - MRI of muscles—to detect abnormal muscles (helpful to take biopsy)
   - Urine for myoglobin in acute cases.

Measurement of CPK is important for the following reasons:

- Very high in dermatomyositis
- Indicates active disease
- To see therapeutic response (reduces after therapy).

Occasionally, CPK may be normal in dermatomyositis:

- If dermatomyositis is associated with internal malignancy
- Due to long standing disease with atrophy of muscles
- Due to the presence of inhibitors in blood.

Causes of high CPK:

- Exercise
- Intramuscular injection
- Muscle trauma or road traffic accident
- Convulsion
- Alcoholism
- Dermatomyositis or polymyositis
- Acute myocardial infarction (CPK-MB)
- Myopathy
- Rhabdomyolysis
- Chronic liver disease (CLD)
- Drugs—statins, busulfan, narcotics, colchicine and chloroquine.

Isoenzymes of CPK:

- MM (mainly in skeletal muscle)
- MB (mainly in cardiac muscle)
- BB (in brain).

Q. What are the **EMG findings** in dermatomyositis?

A. As follows:

- Spontaneous fibrillation (at rest)
- Small amplitude, short duration and polyphasic action potential (after voluntary activity)
- Salvos of repetitive potential on mechanical stimulation of the nerve.

RELATED QUESTIONS AND ANSWERS

Q. What is **polymyositis** or **dermatomyositis**?

A. Polymyositis is the nonsuppurative, noninfective inflammation of skeletal muscle of unknown cause, characterized by necrosis, fibrosis and regeneration of muscles. When associated with **skin rash**, it is called dermatomyositis.

Q. How do you **classify** dermatomyositis or polymyositis?

A. Five types:

1. Adult polymyositis
2. Adult dermatomyositis
3. Dermatomyositis or polymyositis associated with malignancies
4. Childhood dermatomyositis or polymyositis
5. Dermatomyositis or polymyositis associated with other autoimmune rheumatic disease (ARD, e.g. SLE, rheumatoid arthritis, SSc).

Q. What are the **causes** of dermatomyositis?

A. Actual cause unknown. Probable factors are:

- Autoimmune mechanism (presence of anti-Jo-1 antibody and lymphocyte infiltration in muscle).
- Viral (coxsackie B, rubella and influenza have been suggested).
- Associated with malignancy (the most common cause is bronchial carcinoma in male and ovarian carcinoma in female). Dermatomyositis can precede any malignancy of lungs, ovary, breast, stomach.
- Drugs causing polymyositis—penicillamine and zidovudine.

Q. If the patient is **elderly,** what disease should be excluded?

A. Malignancy (bronchial carcinoma, also carcinoma of the breast, GIT and ovary).

Q. What are the **presentations** of dermatomyositis?

A. Common in female, F:M = 2:1, peak incidence is in fifth and sixth decades.

- Muscular weakness, mainly involving the proximal muscles (shoulder and pelvic girdle).
- Skin rash—typically affects upper eyelids with erythema called "Heliotrope rash" (photosensitive, erythematous and scaly). Flat, red rash on face and upper trunk, erythematous rash of knuckles with raised violaceous scaly eruption (Gottron's sign). Erythematous rash also may occur in knee, elbow, malleoli, neck and anterior chest (often a V sign) or back and shoulder (shawl sign).
- Pharyngeal, laryngeal and respiratory muscles involvement may cause dysphagia, dysphonia and respiratory failure.
- Others—arthralgia, arthritis, myalgia and Raynaud's phenomenon.

Note Remember the following points:

- In some patients, only skin rash may be present without muscle involvement called **dermatomyositis sine myositis**
- Ocular involvement is rare
- Malignancy is more in dermatomyositis, less in polymyositis
- The patient may present with acute renal failure because of myoglobinuria secondary to rhabdomyolysis.

Q. How do you **test for proximal myopathy**?

A. As follows:

In the upper limb:

- Ask the patient to raise the arms above the head (patient is unable to do so)
- Ask the patient to sit, keep the arm on side at 90° and press against resistance
- The patient may complain of difficulty in combing, climbing upstairs, rising from the chair.

In the lower limb:

- With the patient lying flat, press the knee and ask the patient to raise the foot against resistance
- Ask the patient to squat, now ask him to stand up (patient is unable to do so).

Q. What are the **causes of proximal myopathy**?

A. Causes are:

- Myopathy (limb girdle, fascioscapulohumeral), except myotonic dystrophy
- Dermatomyositis or polymyositis
- Myasthenia gravis
- Myasthenic myopathic syndrome (Eaton-Lambert syndrome)
- Thyrotoxicosis, also in hypothyroidism
- Cushing's syndrome
- Osteomalacia
- Diabetic amyotrophy
- Hyperparathyroidism
- Drugs—lovastatin, chloroquine, colchicine (all are associated with high CPK). Steroid can cause proximal myopathy (it is not associated with high CPK).

Q. What are the **causes of painful muscle?**

A. Causes are:

- Physiological—after exercise
- Polymyositis
- Polymyalgia rheumatica
- Fibromyalgia syndrome
- Viral infection
- Chronic alcoholism
- Following convulsion
- Functional
- Associated with rheumatological disease.

Q. What are the causes of **acute or sudden muscular weakness?**

A. As follows:

- Gullain Barre syndrome
- Hypokalemia and hyperkalemia
- Familial periodic paralysis
- Thyrotoxic periodic paralysis
- Functional (HCR).

Q. What will be the **deep tendon reflex** in dermatomyositis?

A. Usually intact.

Q. What is the **pathognomonic sign** in dermatomyositis?

A. Heliotrope rash.

Q. What is **heliotrope rash**?

A. It is a violaceous, purple or lilac colored rash, present usually over the upper eyelids. It may also be present on the cheeks, nasal bridge and knuckles. Presence of heliotrope rash is highly suggestive of dermatomyositis. It is derived from the name of the shrub Heliotropium, which has fragmented, purple flowers. It is common in childhood dermatomyositis, also occurs in adults.

Q. What is **Gottron's sign**?

A. It is scaly, purple-red, raised, flat-topped, and vasculitic patches over the extensor surface of joints and knuckles of hands. It may be found on the elbow and knee.

Q. How to **treat** dermatomyositis or polymyositis?

A. As follows:

- Prednisolone 0.5 to 1 mg/kg daily to induce remission. Continued for at least 1 month after myositis is clinically and enzymatically inactive. Then taper the dose slowly. Maintenance dose is 5 to 7.5 mg daily. May be required to continue for months, even years.
- If severe respiratory or pharyngeal weakness—methylprednisolone 1 g daily for 3 days.
- If no response to steroid—methotrexate or azathioprine may be given.
- If methotrexate and azathioprine fail—cyclosporine or cyclophosphamide or mycophenolate mofetil may be tried.
- High-dose IV immunoglobulin may help in some cases.
- Treatment of underlying malignancy may improve the condition.
- Physiotherapy.

Q. What is the **prognosis?**

A. As follows:

- 5 years survival rate in treated patient is > 95%, 10 years survival is 84%.
- Worse prognosis if severe in presentation, delay of treatment, severe dysphagia or respiratory difficulty, older patient and if underlying malignancy.
- Dermatomyositis responds better than polymyositis. So, better prognosis.

Q. What is **Eaton-Lambert syndrome?**

A. It is a paraneoplastic syndrome characterized by proximal muscle weakness and wasting because of defective acetylcholine release at the neuromuscular junction. It commonly involves the lower limb, but may involve any muscle.

Causes:

- There is defect in **acetylcholine** release at the neuromuscular junction that is thought to be due to an auto-antibody against prejunctional voltage gated calcium channel on the motor nerve terminal. Small cell carcinoma of the lung may trigger the auto-antibody reaction.
- It is commonly because of small cell carcinoma of the lung, may be associated with or may precede the manifestations of carcinoma.

Features:

- Proximal weakness, commonly in the lower limbs but any muscle can be involved. Ptosis and diplopia may occur in 70% cases.
- Reflexes are absent or diminished.
- Muscle power may be increased and tendon reflexes may return after repeated activity or sustained contraction of the relevant muscle (reverse of myasthenia gravis).
- Patients may have autonomic dysfunction (dry mouth, constipation, impotence).

Note Long-standing

Abnormality of reflex, muscle power and autonomic disturbance are absent in myasthenia gravis.

Investigations:

- EMG shows progressive incremental response (reverse of myasthenia gravis, where there is decremental response).
- Antibody to P/Q type voltage gated calcium channel (anti VGLC)—found in 90% cases.

Treatment:

- 3, 4 diaminopyridine may be given
- IV immunoglobulin may be helpful
- Pyridostigmine may give symptomatic relief
- Plasmapheresis
- Treatment of the primary cause.

ANKYLOSING SPONDYLITIS

CHIEF COMPLAINTS

- Low back pain for … months.

HISTORY

History of present illness: According to the patient's statement, he was reasonably well … months back. Since then, he has been suffering from low back pain, worse in the morning after waking from sleep that improves with physical activity or exercise. Sometimes, it is worse while sleeping at night. He also feels difficulty in bending forward, backward or to either sides for pain. He does not complain of pain in any other joints. There is no history of pain in the eye, fever, mouth ulcer, palpitation, cough, chest pain, rash, urinary or bowel abnormality.

History of past illness: Nothing significant. There is no history of diarrhea (to exclude IBD), skin problem (to exclude psoriatic arthritis).

Family history: He has 2 brothers and 1 sister. No one in his family is suffering from such illness. No family history of psoriasis or inflammatory bowel disease.

Personal history: Mention according to the patient's statement.

Socio economic history: Mention according to the patient's statement.

Treatment History: He used to take some painkillers during his illness.

GENERAL EXAMINATION

- The patient is slightly emaciated
- Eye—slightly red
- No skin or nail change (to exclude psoriatic arthritis)
- No anemia, jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- Pulse—90/minutes
- BP—120/80 mm Hg.

SYSTEMIC EXAMINATION

Locomotor System

- There is loss of lumbar lordosis, thoracic kyphosis and compensatory hyperextension of neck (in advanced stage, **question mark "?"** or stooped posture).
- The patient is unable to look up and unable to turn to any side without movement of whole body.
- There is restricted movement of spine in all directions (forward, lateral and backward bending).
- SLR is positive.
- The patient is unable to make contact between the occiput and the wall, when standing with heel and back against the wall (ask the patient to stand along the side of the wall with heel and back against the wall, now measure occiput to wall distance. Gap indicates limitation of thoracic and cervical spine).
- Sacroiliitis is present.
- Achilles tendinitis and plantar fasciitis are present.
- Right knee joint is mildly tender and swollen with slight reduction of movement.
- Schober's test is positive.

Respiratory System

- Chest expansion is restricted
- Respiration—abdominal
- Few crepitations over both apical zones (indicates apical fibrosis).

Cardiovascular System

Precordium:

1. Inspection – No abnormality
2. Palpation – No abnormality
3. Auscultation:
   - First heart sound—normal
   - Second heart sound—aortic component is soft
   - There is early diastolic murmur in left lower parasternal area (due to AR).

Abdomen

- Abdomen—looks protruded
- No hepatosplenomegaly
- Kidney—Not ballotable.

Examination of other system reveals no abnormalities.

SALIENT FEATURES

Mr …, 35 years, service holder, normotensive, nondiabetic, nonsmoker, hailing from …, presented with low back pain for ... months that is worse in the morning after waking from sleep that improves with physical activity or exercise. Sometimes, it is worse while sleeping at night. He also feels difficulty in bending forward, backward or to either sides for pain. He does not complain of pain in any other joints. There is no history of pain in the eye, fever, mouth ulcer, palpitation, cough, chest pain, rash, urinary or bowel abnormality. No one in his family was suffering from such illness. No family history of psoriasis or inflammatory bowel disease. He was treated with painkillers by local physicians.

On examination – general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is ankylosing spondylitis.

Q. What are your **differential** diagnoses?

A. Any cause of spondyloarthropathy may be considered as differential diagnosis.

- Reiter's syndrome or reactive arthritis
- Enteropathic arthritis (Crohn's disease and ulcerative colitis)
- Psoriatic arthritis
- Juvenile chronic arthritis (if the patient is less than 16 years old).

Q. What are the **investigations** done in ankylosing spondylitis?

A. As follows:

1. X-ray of SI joints and spine (lumbosacral, dorsal and cervical)

2. MRI of lumbosacral spine may be done in some cases
3. CBC (ESR may be high)
4. CRP (may be high)
5. Rheumatoid factor (negative)
6. HLA-B27 (measured in blood lymphocytes) is positive in 90% of the cases
7. Others according to cause (barium enema and follow through for inflammatory bowel disease).

Note Remember the following:

HLA-B27 is neither necessary not sufficient for diagnosis of AS. However, presence of HLA-B27 increases the probability of AS. In typical AS with absence of HLA-B27, there is probability of IBD.

X-ray shows:

- Sacroiliitis—often the first abnormality, beginning in the lower synovial parts of the joints with irregularity and loss of cortical margins, widening of the joint space and subsequently sclerosis, narrowing and fusion.
- In thoracolumbar spine—squaring of vertebrae due to erosion. Bridging syndesmophytes formation at the outermost fibers of the annulus, results in **bamboo spine appearance.** There may be ossification of anterior longitudinal ligament or interspinous ligament and facet joint fusion.

RELATED QUESTIONS AND ANSWERS

Q. What is **ankylosing spondylitis**? What are the usual **presentations**?

A. It is a chronic inflammatory seronegative arthritis characterized by progressive stiffening and fusion of axial skeleton.

Common in young adult, second and third decade, M:F = 3:1. The patient presents with low back pain with morning stiffness, worse in the morning and with inactivity, pain improves after exercise. Peripheral arthritis occurs in 10% cases.

Q. What is the **nature of arthritis** in ankylosing spondylitis?

A. Inflammatory.

Q. What are the **extra-articular manifestations** of ankylosing spondylitis?

A. As follows:

1. Eyes: Anterior uveitis (iritis) 25%, conjunctivitis 20% (the patient may present with painful red eye and photophobia).
2. Heart:
   - AR (4%, due to aortitis), mitral regurgitation
   - Conduction defect, such as first-degree block, left bundle branch block (LBBB) and atrioventricular block (AV block)
   - Pericarditis.
3. Chest and lungs:
   - Chest pain (pleuritic) and reduced chest expansion (costovertebral joint involvement)
   - Apical upper lobe pulmonary fibrosis, cavitation and later on, aspergilloma may occur
   - Pulmonary hypertension and cor pulmonale.
4. Prostatitis (80%), usually asymptomatic.
5. Neurological: Cauda equina syndrome (there is weakness of lower limb, loss of sphincter and rectal control with saddle sensory loss).
6. Others: Plantar fasciitis, Achilles' tendinitis, amyloidosis and osteoporosis.

Q. What are the diagnostic criteria for AS?

A. The presence of 3 of following 4 indices in adults < 50 years with chronic back pain indicates AS:

- Morning stiffness > 30 minutes
- Improvement of back pain with exercise but not rest
- Awakening because of back pain during second half of the night only
- Alternating buttock pain.

Alternately Modified New York Criteria (1984) is used:

- Low back pain at least 3 months duration increased by exercise relieved by rest
- Limitation of lumbar spine movement in at least 2 planes
- Decreased chest expansion less than normal
- Bilateral sacroiliitis grade 2 to 4
- Unilateral sacroiliitis grade 3 to 4.

Definite AS—sacroiliitis with any clinical criteria.

Note Remember the following :

MRI is more sensitive than X-ray.

Q. What is the cause of chest pain in ankylosing spondylitis?

A. Chest pain is due to costochondral junction involvement.

Q. What are the types of ankylosing spondylitis?

A. Two types:

- Primary- without any other association
- Secondary- when associated with other seronegative arthritis.

Q. What are the other causes of sacroiliitis?

A. Any cause of spondylo-arthropathy.

Q. What is spondylo-arthropathy or spondarthritis?

A. It is a group of inflammatory arthritis characterized by:

1. Seronegative rheumatoid factor (RA test is negative)
2. Sacroiliitis and inflammatory spondylitis
3. Asymmetrical inflammatory oligoarthritis (lower > upper limbs, bigger joints are involved)
4. Inflammatory enthesitis
5. Absence of nodules and other extra-articular features of rheumatoid arthritis
6. Typical overlapping extra-articular features:
   - Mucosal inflammation (such as conjunctivitis, buccal ulceration, urethritis, prostatitis, bowel ulceration)
   - Pustular skin lesions and nail dystrophy
   - Anterior uveitis
   - Aortic root fibrosis (AR, conduction defects)
   - Erythema nodosum
7. Familial association (high in HLA-B27).

Q. What are the diseases in spondylo-arthropathy?

A. As follows:

- Ankylosing spondylitis
- Reiter's syndrome or reactive arthritis

- Enteropathic arthritis (in Crohn's disease and ulcerative colitis)
- Psoriatic arthritis.

Q. What is **enthesopathy**?

A. Inflammation at the ligamentous attachment with erosion of adjacent bone. Healing of such lesion at the junction of intervertebral disk and vertebral bodies causes new bone formation, called syndesmophyte (**hallmark** of ankylosing spondylitis).

Q. What is the **natural history** of ankylosing spondylitis?

A. Up to 40% may develop severe spinal restriction, 20% may have significant disability. Early peripheral joint disease, especially hip joint involvement indicates poor prognosis.

Q. How would you perform **genetic counseling** with this patient?

A. If the patient is HLA-B27 positive, there is 30% chance for the siblings to develop ankylosing spondylitis.

Q. How **Schober's test** is performed?

A. As follows:

- Mark the points in midline 10 cm above and 5 cm below a line joining the 'Dimple of Venus' on the sacral promontory (the line passes along the L_5 spinous process between the posterior superior iliac spines).
- Ask the patient to bend forward as far as possible.
- Now measure the distance between upper and lower markings.

Normally, it increases by > 5 cm below 50 years of age. If it is < 5 cm, it indicates limitation of mobility of spine.

Modified Schober's test: Only the upper marking is taken that is sufficient for the test, as the lower part is remaining fixed. It is called modified Schober's test.

Q. How to **differentiate** between mechanical and inflammatory arthritis?

A. As follows:

Features	Mechanical arthritis	Inflammatory arthritis
1. Age	Any, 15~90 yrs	Below 40 yrs
2. Onset	Acute	Insidious, > 3 months
3. Family history	No	Usually positive
4. Exercise	Worse	Improved
5. Rest	Better	Worse
6. Morning stiffness	No	Positive
7. Sleep disturbance	No	Yes
8. Neurological signs	May be present	No
9. Range of movement	Asymmetrical	Symmetrical
10. Straight leg raise (SLR)	Positive	Normal

Q. How to **differentiate** aortic regurgitation of rheumatic heart disease and of ankylosing spondylitis?

A. From history and echocardiogram:

- In rheumatic heart disease, echocardiogram shows the involvement of valve cusps (shortening, thickening and fusion).
- In ankylosing spondylitis, echocardiogram shows involvement of aorta or aortic root dilatation due to aortitis.

Q. What are the **differences between** syndesmophyte and osteophyte?

A. As follows -

Syndesmophyte	Osteophyte
1. Secondary to inflammatory disease	1. Degenerative
2. Due to endochondral calcification of the annulus fibrosus	2. New bone at the corners of the vertebra
3. It grows longitudinally (above or below) causing bridging of adjacent vertebra	3. It grows horizontally outwards
4. Hallmark of ankylosing spondylitis	4. Hallmark of osteoarthrosis

Q. What are the **causes of death** in ankylosing spondylitis?

A. Causes are:

- Amyloidosis
- Spinal fracture, especially in cervical spine leading to quadriplegia.

Q. How to **treat** ankylosing spondylitis?

A. As follows:

- Exercise is the mainstay. The patient must remain active. Swimming is the best activity
- Prolong sitting or inactivity should be avoided
- NSAID to relieve pain
- Physiotherapy
- DMARDs—sulfasalazine or methotrexate (MTX) are helpful in peripheral arthritis, but have no effect on axial disease
- In patient with persistent active inflammation, anti-TNF drug therapy may be helpful for both spinal and peripheral arthritis
- Local steroid injection may be given for persistent plantar fasciitis, other enthesopathies and peripheral arthritis
- Oral steroid may be needed for acute uveitis
- Orthopedic measures—may be needed for severe hip, knee or shoulder restriction.

Q. What is the **prognosis**?

A. With appropriate treatment, the prognosis is usually excellent and there is minimum disability unless the hip joints are involved. Around 80% patients remain fully employed.

Note Remember the following points:

- Disease is mild in women. Peripheral arthritis is more in women. Spinal arthritis is less
- May be severe, when it affects in early age, also worse prognosis
- Hip joint involvement is more in teen age
- In the past, radiotherapy was given that is not used nowadays, because there is 10-fold increase incidence of leukemia (AML).

Radiographycally, AS may confused with Alkaptonuria, DISH, lumbar spondylosis and Osteitis condensans ilii.

- In alkaptonuria, calcification looks like AS. But there is calcification of intervertebral disk in Alkaptonuria, never in AS.
- Diffuse idiopathic skeletal hyperostosis (DISH)—florid new bone formation along the anterolateral aspects of at least four contiguous vertebral bodies. In DISH, calcification gives the appearance of **flowing wax** on the anterior body of vertebrae. Sacroiliac and apophyseal joints are normal in DISH. It occurs in middle age and elderly, usually asymptomatic.
- In lumbar spondylosis, there is disk space narrowing and marginal sclerosis.
- In osteitis condensans ilii, there is sclerosis on the iliac site of sacroiliac joints, confuses with sacroilütis. It is a postpartum radiographic finding.

SYSTEMIC SCLEROSIS

CHIEF COMPLAINTS

- Thickening and tightness of skin for … months
- Pain and swelling of multiple joints for … months
- Difficulty in deglutition for … months.

HISTORY

History of present illness: According to the statement of the patient, she was reasonably well … months back. Since then, she noticed gradual thickening and tightening of the skin on the dorsum of her hands that causes difficulty in movement of fingers and wrist joints. After a few months, she noticed the same changes involving her face causing difficulty in opening her mouth. On enquiry, she admitted that her fingers change color and sequentially become pale, blue and red, on exposure to cold water or weather. She also complains of pain and swelling of multiple joints including both knee joints, wrist joints and small joints of hand for last … months. It is not associated with morning stiffness and improves on rest. The patient also complains of occasional heartburn, difficulty in deglutition, loss of appetite and significant loss of body weight for... months. There is no history of fever, shortness of breath, cough, pain abdomen, oral ulcer, skin rash or dryness of eyes or mouth. Her bowel and bladder habits are normal.

History of past illness

Family history: There is no such illness in the family

Personal history

Drug and treatment history

Menstrual history

Socioeconomic history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient ill looking and emaciated.
- The face is smooth, shiny, tight, and immobile with hypopigmented and pigmented areas (salt and pepper appearance). There is loss of wrinkling of forehead. The nose is pinched up and tapered (beaking of nose, bird beak face). There is puckering of skin around the lips with a small orifice of mouth (microstomia). The patient has difficulty in opening the mouth. Multiple telangiectasias are noted (mention the location)
- The skin of both hands is smooth, shiny, tight, thick and edematous with pigmented and hypopigmented area. The skin of legs, chest and other parts of the body is normal.
- Mildly anemic.
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema.
- No lymphadenopathy or thyromegaly.
- Pulse—84/min.
- BP—120/75 mm Hg.
- Temperature—98.6^0 F.

SYSTEMIC EXAMINATION

Musculoskeletal System

1. **Hands:**
   - The skin of both hands is smooth, shiny, tight, thick and edematous with pigmented and hypopigmented area
   - Interphalangeal (IP) and metacarpophalangeal joints of both hands are swollen with flexon contracture
   - There is sclerodactyly (tapering of fingers) and infarction (or ulcer or gangrene) at the tip of the fingers and atrophy of pulp
   - Telangiectasia at the base of nails
   - (Also, look for resorption, beaking of the nails called pseudoclubbing due to resorption, and amputation of finger. Also mention if hard nodule or calcinosis seen over any finger).
2. **Joints:** Both knee joints and both wrists are swollen and tender.
3. **Muscles:** Generalized wasting is present.

Examination of other systems reveals no abnormalityies.

SALIENT FEATURES

Mrs …, 41 years, housewife, normotensive, nondiabetic, nonsmoker, hailing from …, presented with gradual thickening and tightening of the skin on the dorsum of her hands for … months that causes difficulty in movement of fingers and wrist joints. After a few months, she noticed the same changes involving her face causing difficulty in opening her mouth. On enquiry, she admitted that her fingers change color and sequentially become pale, blue and red, on exposure to cold water or weather. She also complains of pain and swelling of multiple joints including both knee joints, wrist joints and small joints of hand for last … months. It is not associated with morning stiffness and improves on rest. The patient also complains of occasional heartburn, difficulty in deglutition, loss of appetite and significant loss of body weight for ... month**.** There is no history of fever, shortness of breath, cough, pain abdomen, oral ulcer, skin rash or dryness of eyes or mouths. Her bowel and bladder habits are normal. There is no family history of such illness. She was treated with different creams and ointments, the name of that she could not mention.

On examination, general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is systemic sclerosis.

Q. In this case, what **specific questions** did you ask?

A. I have asked the following questions:

- Whether any change of color in her finger on exposure to cold? (Raynaud's phenomenon)
- If yes, what colors are they? (Pallor, cyanosis and redness).
- Is there any difficulty in swallowing?
- Is there any difficulty in breathing?
- Is there any bowel abnormality? (occasional diarrhea or constipation.)

Q. If patient complains of **difficulty in deglutition**, what is the likely cause?

A. CREST syndrome.

Q. What is **CREST** or **CRST** syndrome? What questions should be asked in CREST syndrome?

A. It is a syndrome characterized by:

- **C: C**alcinosis
- **R: R**aynaud's phenomenon
- **E: E**sophageal involvement (dysphagia)
- **S: S**clerodactyly
- **T: T**elangiectasia.

Ask about Raynaud's phenomenon and dysphagia. CREST syndrome is also called limited cutaneous systemic sclerosis, with a better prognosis. Anti-centromere antibody is present in serum in 70% to 80% cases (if diffuse deposition of calcium in subcutaneous tissue with presence of acrosclerosis, it is called Thibierge-Weissenbach syndrome).

RELATED QUESTIONS AND ANSWERS

Q. What is **systemic sclerosis**? What are the **presentations**?

A. It is a connective tissue disease characterized by fibrosis and degenerative changes in skin, vasculature and internal organs. Common in female (F:M = 4:1), age 30 to 50 years. Usual presentations are:

- Raynaud's phenomenon—90 to 97% cases. May proceed by months or years before other symptoms.
- Tightening and thickening of the skin of hands and other parts of the body, arthralgia and arthritis (nonerosive inflammatory), heartburn (reflux esophagitis due to hiatus hernia), dysphagia, odynophagia, occasional diarrhea and constipation (blind-loop syndrome) and shortness of breath (DPLD).

Two types of systemic sclerosis:

- Diffuse cutaneous systemic sclerosis (DCSS, 30%)—skin involvement of trunk and extremities above the knee and elbow. Initially, skin is edematous, thick and tight. Raynaud's phenomenon may occur just before or with skin symptoms. DPLD and renal involvement are more in DCSS, who have topoisomerase 1 antibody.
- Limited cutaneous systemic sclerosis (LCSS, 70%)—skin involvement only at the extremities. Hands, feet or forearm may be involved. Raynaud's phenomenon may occur before skin change. Face may be involved. CREST is a localized type of systemic sclerosis. Pulmonary hypertension is more common in limited disease.

Other varieties (localized):

- Scleroderma sine scleroderma—involves internal organ without skin lesion
- Morphea—localized, well demarcated, indurated or plaque with central hypopigmentation and tethering of skin, usually in extremities and face
- Linear—if skin involvement is in a linear pattern, usually in lower limbs.

Pathology or pathogenesis in systemic sclerosis:

- Vascular change—widespread vascular damage in arteries, arterioles and capillaries. There is intimal proliferation, vessel wall inflammation, and endothelial damage with release of cytokines and endothelin-I, the later cause vasoconstriction. Also, platelet activation.
- Fibrotic change—fibroblast synthesize collagen I and III, fibronectin, glycosaminoglycans, producing fibrosis in dermis and internal organs.

- Humoral immunity—increased during T-lymphocyte and complement activation, autoimmunity and autoantibody production to nuclear antigen.

Histological findings of skin biopsy in systemic sclerosis:

- Thinning or absence of epidermis
- Excess collagen and fibrosis of dermis, loss of appendages in dermis, perivascular infiltration of chronic inflammatory cells (lymphocytes and plasma cells) and intimal proliferation and obliteration of blood vessels.

Q. What **investigations** would you do in systemic sclerosis?

A. Diagnosis is usually clinical. The following investigations may be done:

1. Complete blood count (ESR is high, but CRP is usually normal unless there is severe organ involvement or coexisting infection).
2. Serology:
   - RA test (positive in 20% to 30% cases)
   - ANA (positive in 70% cases)
   - Anti-topoisomerase 1 or anti-Scl-70 (positive in 30% in diffuse type)
   - Anti-centromere antibody (positive 60% in CREST and 10% in diffuse systemic sclerosis) with a speckled nucleolar pattern.
3. Skin biopsy for histopathology.
4. Others:
   - Urine R/E (may be proteinuria)
   - X-ray of the hands (deposition of calcium around the fingers, erosion, resorption of phalanges and disorganization of joints)
   - Chest X-ray (DPLD and honeycomb lung)
   - CT scan of the chest (to detect DPLD)
   - Lung function tests (restrictive lung disease)
   - Barium swallow (dysmotility or reduction of peristalsis, narrowing and dilatation. Hiatus hernia may be present, detected by barium swallow X-ray in Trendelenburg position)
   - Barium follow through
   - Motility study may be done
   - Electrocardiogram (ECG)
   - IgG level (raised).

Q. What are the **changes** in the different systems of the body?

A. As follows:

1. Skin changes:
   - Hands—initially non-pitting edema of fingers and flexor tendon sheaths. Then skin becomes shiny, thick and tight, distal skin creases disappear. There is erythema and tortuous dilatation of capillary loops in nail fold bed.
   - Face and neck—thinning of lips, furrowing, microstomia.
   - Skin in other parts of the body (thick, tight, hyper or hypopigmented and vitiligo).
   - Skin of the chest is tight and thick.
   - Skin score is calculated by Rodnan total skin score.
2. Raynaud's phenomenon: It may lead to critical tissue ischemia, skin ulceration over pressure areas, infarction and pulp atrophy at finger tips.
3. Joints and muscles: Arthralgia, morning stiffness, flexor tenosynovitis, flexion contracture or deformity. Proximal or distal muscle weakness and wasting.
4. Gastrointestinal:

- Esophagus—50% involvement. Dysphagia and odynophagia may be because of reflux esophagitis, sliding hiatus hernia, constriction or secondary achalasia, and dysmotility or reduction of peristalsis. Esophageal manometry shows abnormal and reduced peristalsis in 90%.
- Stomach—early satiety, gastric outlet obstruction and recurrent occult upper gastrointestinal tract bleeding causing "**watermelon stomach**" (antral vascular ectasia in 20% cases).
- Intestine—hypomotility, bloating, distension, intestinal obstruction or pseudo-obstruction, blind-loop syndrome, diarrhea and wide-mouth diverticula in colon. Rarely, a serious disorder called **pneumatosis cystoides intestinalis,** in which there is radiolucent cyst or streaks in the wall of small intestine due to air in the intestinal wall can occur. The patient presents with severe abdominal pain. It is detected by plain X-ray abdomen.

5. Liver: Primary biliary cirrhosis (PBC) may be associated.
6. Respiratory:
   - DPLD, pulmonary hypertension and cor pulmonale. Pulmonary hypertension may occur without parenchymal lung disease due to pulmonary vessel involvement. It is six times more common in limited type than diffuse type.
   - Others—pneumonitis, rarely pleural effusion and alveolar cell carcinoma.
7. Heart—Dysrhythmia, conduction defect, heart failure, cardiomyopathy, myocardial fibrosis and pericardial effusion.
8. Kidneys (20% involvement):
   - Renal failure in advanced stage (often fatal)
   - Malignant hypertension (difficult to control, may respond to angiotensin-converting enzyme inhibitors).
9. Endocrine:
   - Hypothyroidism (due to thyroid gland fibrosis)
   - Impotence.
10. Neurologic:
    - Entrapment neuropathy
    - Facial nerve palsy
    - Autonomic dysfunction.

Q. How to **manage** systemic sclerosis?

A. There is no specific therapy.

1. General management for Raynaud's phenomenon:
- Exposure to cold should be avoided (by the use of gloves or mittens), lubricants should be used (to avoid dryness).
- Smoking should be stopped, regular exercise and massage of skin, cleanliness of digital ulcer.
- Drugs to be avoided (beta-blocker, ergotamine, oral contraceptive and sympathomimetic).
- Antiplatelet (aspirin) may be given.
- Calcium antagonist (diltiazem and nifedipine), ACE inhibitor, angiotensin II receptor blocker (valsartan) may be effective.
- If no response or in severe case, prostacyclin analog epoprostenol infusion intermittently.
- If still no response, then surgery (digital sympathectomy and microsurgical revascularization), lumbar sympathectomy, thoracic sympathectomy under video assisted thoracic surgery. If needed, amputation of fingers or toes.
- Antibiotic may be needed, if there is infection on ulcerated skin lesions. Higher doses should be given since tissue penetration is poor in scleroderma.

2. For arthritis—Non-steroidal anti-inflammatory drugs (NSAIDs).

3. Steroid and cytotoxic drugs may be used, if myositis or alveolitis.

4. Other drugs that have shown no proven benefit, but may be tried are:
   - Penicillamine—reduces cross-linking of collagen (acts as anti-fibrotic)
   - Methotrexate (given in a weekly dose of 7.5 to 15 mg)
   - Cyclosporin or interferon-γ. Recombinant human relaxin therapy (subcutaneously).
5. Other therapy: According to the involvement of the organ.
   - Physiotherapy
   - If DPLD—cyclophosphamide or azathioprine combined with low dose steroid
   - Hypertension—ACE inhibitor may be given
   - Pulmonary hypertension—oral vasodilator, warfarin and oxygen. In advanced case, prostacyclin therapy (inhaled, subcutaneous or intravenous) or oral endothelin receptor antagonist (bosentan, sitaxsentan) should be given
   - Right heart failure—symptomatic treatment with diuretic, digoxin, etc. Heart lung or single lung transplantation in selected cases
   - For reflux esophagitis—proton pump inhibitor and prokinetic drugs
   - For blind-loop syndrome—broad spectrum antibiotic is useful
   - If renal involvement—ACE inhibitor may be helpful
   - Myositis—corticosteroid and cytotoxic drugs may be needed.

Q. What is the role of **steroid**?

A. Steroid has little or no role in the treatment of scleroderma. It can be given in low doses (10 mg/day) with cyclophosphamide if the patient has associated DPLD or myositis.

Prognosis of systemic sclerosis**:** Depends on type, age, sex, involvement of internal organ and extent of skin involvement.

Bad prognostic factors are:
- Diffuse cutaneous systemic sclerosis
- Elderly patient
- Male sex
- Involvement of internal organs (especially kidney, lung and heart). Proteinuria, high ESR, low gas transfer of carbon monoxide and pulmonary hypertension.

Limited cutaneous systemic sclerosis (CRST or CREST):
- Prognosis is relatively better
- Usually mild
- 70% show 10-year survival
- Pulmonary hypertension may develop later on.

Diffuse type:
- 70% show 5-year survival
- Death due to cardiac, renal and pulmonary involvement.

Q. What are the **differential diagnoses** of systemic sclerosis or thickened skin?

A. Scleroderma-like thickening of skin, secondary to some other diseases is called **pseudo-scleroderma.** The causes are:
- Scleroderma
- Scleromyxedema
- Eosinophilic fasciitis or eosinophilic myalgia syndrome
- Amyloidosis
- Graft-versus-host disease (GVHD)
- Diabetic cheiroarthropathy
- Acromegaly

- Porphyria cutanea tarda
- Carcinoid syndrome
- Toxic oil syndrome
- Chemically induced (pentazocine, bleomycin and vinyl chloride).

Scleroedema: It is a disease characterized by painless, edematous induration of face, scalp, neck, trunk and upper part of the extremities. There is no involvement of the hands and feet. Common in children, may be associated with streptococcal infection, usually self-limiting, resolves in 6 to 12 months.

Mixed connective tissue disease (MCTD):

When localized systemic sclerosis coexisting with SLE, polymyositis and rheumatoid arthritis, it is called MCTD. This overlap syndrome is associated with high titer of anti-RNP.

The patient usually presents with Raynaud's phenomenon, myalgia and swollen finger. Later, features, such as sclerodactyly, calcinosis, cutaneous telangiectasia develop. Skin rash of SLE or dermatomyositis, pulmonary fibrosis, pulmonary hypertension, Sjogren's syndrome, may develop later. Prognosis is good.

Treatment: Good response to steroid.

JUVENILE IDIOPATHIC ARTHRITIS (JIA)

CHIEF COMPLAINTS

- Pain and swelling of multiple joints for … months
- Weight loss for … months
- Fever and anorexia for … months.

HISTORY

History of present illness: According to the statement of the patient, he was alright … months back. Since then, he has been suffering from pain and swelling of multiple joints, including the right knee, right ankle, small joints of both hands and both wrist joints. The pain was initially mild, associated with morning stiffness that persists for 2 hours, worse after taking rest and improves with exercise. It is gradually more severe, associated with swelling of the joints. For the last ... days, pain is so severe that it interferes with his daily activities. He also complains of continued low grade fever, substantial weight loss, malaise and anorexia for the last … months. There is no history of mouth ulcer, skin rash, photosensitivity, eye problems, breathlessness, cough, chest pain or alopecia.

History of past illness

Family history: All the family members are of good health. No such illness in the family.

Personal history

Drug and treatment history

Menstrual history

Socioeconomic history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient looks anxious and emaciated
- Moderately anemic
- Skin is normal, no rash
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- Pulse—88/min
- BP—110/80 mm Hg
- Temperature—99° F.

SYSTEMIC EXAMINATION

Musculoskeletal System

Examination of hands:

1. **Inspection:**
   - There is wasting of thenar and hypothenar muscles. No atrophy, ulcer, infarction, gangrene or rash.
   - Wrist joints are swollen. PIP joints of both hands are spindle shaped. There is mild flexion deformity of fingers on right hand.
   - Movement is restricted in the right wrist and fingers with slightly impaired functional activity.

2. Palpation:

- The joints of both hands are tender
- Synovial thickening is present in right wrist.

Examination of right knee joint:

- The right knee joint is swollen, more marked above the patella
- Skin is red and shiny
- Local temperature is raised and the joint is tender
- There is restricted movement on right knee.

Examination of other joints:

- Right ankle is swollen and tender.

Examination of eyes:

- No redness, no nodule.

Examination of respiratory system:

- Normal.

Examination of CVS:

- No abnormality detected.

Examination of the nervous system:

- No evidence of peripheral neuropathy, carpal tunnel or tarsal tunnel syndrome.

Examination of abdomen:

- There is no organomegaly.

SALIENT FEATURES

Mr …, 15 years, student, normotensive, nondiabetic, hailing from …, presented with pain and swelling of multiple joints, including the right knee, right ankle, small joints of both hands and both wrist joints for ... months. The pain was initially mild, associated with morning stiffness that persists for 2 hours, worse after taking rest and improves with exercise. It is gradually more severe, associated with swelling of the joints. For the last ... days, pain is so severe that it interferes with his daily activities. He also complains of continued low grade fever, substantial weight loss, malaise and anorexia for the last … months. There is no history of mouth ulcer, skin rash, photosensitivity, eye problems, breathlessness, cough, chest pain or alopecia. There is no such illness in the family. He used to take painkiller tablet frequently.

On examination, on general examination (mention as above).

On systemic examination (mention as above. Always never forget to mention the extra-articular features).

My diagnosis is JIA.

Q. What are your **differential diagnoses?**

A. As follows:

- Rheumatic fever
- Seronegative arthritis

- SLE
- Viral arthritis
- Acute leukemia.

Q. Could it be **rheumatic fever**?

A. Unlikely, because in rheumatic fever, there is no deformity of joints and wasting of muscles. Moreover, rheumatic fever is diagnosed by major and minor criteria (rheumatic fever licks the joints and kills the heart).

Q. What **investigations** should be done in JIA?

A. As follows:

- Complete blood count (leukocytosis in Still's disease, may be lymphocytosis, thrombocytosis and high ESR)
- CRP (high)
- RA test (usually negative, positive in 10% cases)
- ANA, Anti-ds DNA if SLE is suspected
- X-ray of the joint involved
- Other investigations—to exclude other diseases (according to history).

RELATED QUESTION AND ANSWERS

Q. What is **JIA?**

A. It may be defined as onset of arthritis before 16 years of age and persisting for more than 3 months.

Q. Why there is **wasting** of muscles in JIA?

A. Disuse and release of cytokines (interleukin 1, 6 and TNF).

Q. What are the **causes of acute arthritis in children**?

A. As follows:

- Rheumatic fever
- JIA
- Infections (bacterial and viral)
- Acute leukemia
- Henoch-Schonlein purpura.
- Hemophilic arthritis
- Reactive arthritis
- Others are sickle cell disease, psoriatic arthritis, SLE, osteomyelitis and hypermobility syndrome.

Q. What are the **types** of JIA?

A. As follows:

1. Systemic onset (**Still's disease**)—10% to 15% cases.
2. Oligoarthritis (pauciarticular)—It is of 2 types:
   - Oligoarthritis (persistent)—common (50% to 60%), four or less joints are affected, mainly knee, ankles and wrists, in asymmetrical pattern. Common in girls, 3 years of age. Uveitis may occur. Relatively good prognosis.
   - Oligoarthritis (extended)—occurs in 25% cases, arthritis of many joints may develop after 6 months. This can be very destructive.
3. Polyarticular JIA—involvement of more than four joints, 30% to 40% cases of JIA. It is of 2 types.
   - RA test is positive—affects girl above 8 years. Small joints of hands, wrist, ankle, feet, etc. are involved, later larger joints are involved. Can be very destructive.

- RA test is negative—affects more in girls < 12 years, but may be in any age. Joints involvement like RA positive type, but cervical spine, temporomandibular joint and elbows may be involved. ANA may be positive with chronic uveitis.

4. Other types of juvenile arthritis:
   - Enthesitis-related JIA
   - Psoriatic arthritis
   - Unclassified.

Q. What are the **features** of systemic onset JIA (Still's disease)?

A. As follows:

- Arthritis—involving knee, wrist and ankle. Other joints may be involved.
- High fever—intermittent type, may be continuous.
- Skin rash—appears with fever and disappears when fever subsides. These are macular or maculopapular, Salmon pink color rashes (**Salmon rash**).
- Extra-articular features—hepatosplenomegaly and lymphadenopathy (common). There may be pericardial effusion, pleural effusion and disseminated intravascular coagulation (DIC).
- In chronic cases—micrognathia (small mandible), fusion of cervical spine and retardation of growth.

Q. How to **treat** JIA?

A. As follows:

1. To relieve pain: NSAID
2. General measures:
   - Rest during pain and passive movement of the limb to prevent contracture
   - Physiotherapy
   - Explanation and reassurance to the parents, also to the patient
3. In severe cases—Steroid, preferably alternate days. Pulse methylprednisolone may be given, followed by methotrexate (steroid may cause early fusion of epiphysis resulting in short stature. Even 3 mg prednisolone daily may cause this effect.)
4. Disease modifying drugs should be given in all cases:
   - Methotrexate—5 mg weekly (increase the dose gradually)
   - Sulfasalazine—30 to 50 mg/kg, effective in enthesitis related JIA
   - Others—IV immunoglobulin, cyclosporin and cytotoxic drugs (cyclophosphamide, chlorambucil and azathioprine) may be tried
   - If methotrexate fails—anti-TNF may be given (helpful in all cases, except in systemic onset type, where results are variable). Etanercept may be used
5. Orthopedic surgery, if needed.

Note Remember the following:

If aspirin is used for fever or arthritis, associated with viral infection like influenza below 12 years of age, it may cause Reye's syndrome. So, it should be avoided.

ADULT STILL'S DISEASE

It is a disease of unknown cause characterized by high fever, seronegative arthritis, skin rash and polyserositis. Usually, it is diagnosed by exclusion of other diseases. Commonly occurs in young adults between 16 and 35 years of age, rarely after 60 years.

Diagnostic criteria of Adult Still's disease:

Each of the 4 criteria:

- Quotidian fever, more than 39°C
- Arthralgia or arthritis (knee, wrist and ankle)
- Rheumatoid factor is negative
- ANF is negative.

Plus 2 of the following:

- Leukocytosis > 15 × 10^9/L (usually very high, may be > 40,000)
- Evanescent macular or maculopapular rash, Salmon colored, non-pruritic (common in chest and abdomen)
- Serositis (pleurisy or pericarditis)
- Hepatomegaly
- Splenomegaly
- Lymphadenopathy (usually cervical, may be generalized).

High fever with chill and sweating is very common. Initially arthritis may be mild.
Other features—abdominal pain, myalgia and sore throat.

Investigations:

- CBC (low hemoglobin, high ESR and leukocytosis)
- CRP (is high)
- RA and ANF (are negative)
- Serum ferritin is very high (> 10,000)
- Fibrinogen level (high)
- AST and ALT (high).

Treatment:

- NSAID (high dose aspirin—1 g 8 hourly). Other NSAIDs—indomethacin, ibuprofen may be helpful. NSAID may be effective in 50% cases.
- If no response—high dose prednisolone (60 to 100 mg/day). When the fever subsides, reduce the dose slowly. Steroid is necessary in 50% cases.
- Other drugs—chloroquine, hydroxychloroquine, methotrexate, sulfasalazine, azathioprine and cyclophosphamide may be tried.
- In chronic case, anti-TNF, such as Enbrel (etanercept) or anakinra (interleukin-1 receptor agonist) may be considered.

Note Remember the following:

Recurrent episode occurs in one-third cases.

HEMOPHILIC ARTHRITIS

CHIEF COMPLAINTS

- Recurrent pain and swelling of both knee joints for … years
- Prolonged bleeding following any injury for … years
- Weight loss for … months.

HISTORY

History of present illness: According to the statement of the patient, he was alright … years back. Since then, he has been suffering from recurrent pain and swelling of both knee joints. Initially, only the right knee was involved, persisted for 3 to 4 weeks. After 3 months, both knee joints were involved and the attack persisted for 2 months. Each episode is preceded by mild to moderate physical exertion like playing in the field or trauma. Pain is very severe, aggravates even on slight movement of the joint and improves on rest or hot compression. There is also difficulty in walking, but no history of morning stiffness. Other joints were never involved. The patient agreed that there is prolong bleeding following any minor injury since his childhood. For the last ... months, he is also suffering from fatigue and weakness and has lost some weight. There is no history of fever, gum bleeding or any other bleeding manifestation, skin rash, photosensitivity or bowel or bladder abnormality.

History of past illness: There is prolonged bleeding following any cut injury.
Personal history: Mention according to the patient's statement.
Drug and treatment history: Mention according to the patient's statement.
Family history: One of his maternal uncles has similar disorder since his childhood. He has one brother and one sister. None of them has such illness.
Socioeconomic history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient looks anxious
- Moderately anemic
- Skin is normal. There is no rash
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- No bony tenderness
- Pulse—88/min
- BP—110/80 mm Hg
- Temperature—97^0 F.

SYSTEMIC EXAMINATION

Musculoskeletal System

Knee joints:

1. **Inspection:**
   - Both knee joints are swollen, erythematous and deformed, right one more than the left
   - Muscle wasting is present around both knee joints, more over the right knee
   - There are few ecchymosis of various sizes over the right thigh.

2. Palpation:
- Both knee joints are warm and tender
- Patellar tap is positive
- Movement is restricted.

Other joints: No abnormality.

Gastrointestinal System

- No gum hypertrophy
- There is no organomegaly.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Master …, 12 years, student, normotensive, nondiabetic, hailing from …, presented with recurrent pain and swelling of both knee joints for … years. Initially, only the right knee was involved, persisted for 3 to 4 weeks. After 3 months, both knee joints were involved and the attack persisted for 2 months. Each episode is preceded by mild to moderate physical exertion like playing in the field or trauma. Pain is very severe, aggravates even on slight movement of the joint and improves on rest or hot compression. There is also difficulty in walking, but no history of morning stiffness. Other joints were never involved. The patient agreed that there is prolong bleeding following any minor injury since his childhood. For the last ... months, he is also suffering from fatigue and weakness and has lost some weight. There is no history of fever, gum bleeding or any other bleeding manifestation, skin rash, photosensitivity or bowel or bladder abnormality. He has history of prolong bleeding following circumcision. One of his maternal uncles has similar disorder since his childhood.

On examination, on general examination (mention as above).

On systemic examination (mention as above).

With this history and physical findings, I have some differential diagnoses:
- Hemophilic arthritis (due to hemophilia A)
- Christmas disease with arthritis.

Q. What are the other possible **diagnoses**?

A. As follows:
- Juvenile idiopathic arthritis (JIA)
- Acute leukemia.

Q. **Why** not JIA?

A. There is history of persistent bleeding following any injury that is against JIA.

Q. Can it be **rheumatic fever**?

A. No. Because rheumatic fever is diagnosed by major and minor criteria that are not present in this case. Also there is persistent bleeding and deformity of joints that are against rheumatic fever.

Q. Which **joints are commonly involved** in hemophilic arthritis?

A. Commonly knee, elbow, ankle and hip joints are involved.
- In infants—hip joint is commonly involved
- In older children—knee joint is commonly involved.

Q. What is the **cause of joint deformity** in hemophilia?

A. It is due to secondary osteoarthrosis and wasting of the muscles around the joint.

Q. What are the **causes of hemarthrosis?**

A. As follows:

- Trauma
- Hemophilia
- Christmas disease
- Von Willebrand disease
- Sickle cell disease
- Excess anticoagulant
- Rarely, malignancy.

RELATED QUESTIONS AND ANSWERS

Q. What are the **presentations of hemophilic arthritis**?

A. Hemarthrosis occurs when plasma level of factor VIII: C is < 1%. Arthritis may be spontaneous without trauma or may follow even minor trauma.

- Initially—tingling, abnormal sensation, stiffness and instability of the joint.
- Later on—the joint is red, hot, swollen and painful.

Repeated hemarthrosis may cause:

- Synovium hypertrophy
- Fibrotic change in synovium
- Destruction of cartilage
- Reduction of joint space
- Subchondral cyst formation
- Bone shows erosion, marginal sclerosis, osteophyte formation and ankylosis of joint.

Q. What are the **radiological signs** in hemophilic arthritis?

A. As follows:

- Initially—joint space is increased and widening of intercondylar notch occurs (in knee joint, indicates long standing hemorrhage).
- Later on- reduction of joint space, periarticular osteopenia, marginal sclerosis, subchondral cyst formation, secondary osteoarthrosis (with osteophyte) and ankylosis of joint.

Q. What are the **causes of widening of intercondylar notch**?

A. As follows:

- Hemophilia
- Christmas disease
- Long standing effusion in knee joint.

Q. How to **treat** hemophilic arthritis?

A. As follows:

- Complete rest, elevation of the affected limb and immobilization by splinting.
- Analgesic may be given (paracetamol or acetaminophen or codeine). Aspirin or other NSAIDs are contraindicated (as they interfere with platelet function and may cause excess bleeding).
- Factor VIII transfusion—20 to 30 IU/kg. Repeated after 12 hours and also after 24 and 36 hours (higher dose is required, if treatment is delayed).

- Once acute stage is over, the patient should be mobilized and physiotherapy should be started (isometric exercise, followed by active movement, hydrotherapy).
- Arthrocentesis (aspiration from joint) is rarely necessary.

Brief Discussion About Hemophilia

Q. What is **hemophilia**?

A. It is an X-linked inherited disorder because of deficiency of factor VIII or anti-hemophilic factor, characterized by prolonged bleeding. Usually female is the carrier and male is the sufferer. There is high rate of new mutations, in 30%, there is no family history.

Q. What are the **types** of hemophilia?

A. Normal factor VIII level is 50 to 150 IU/dL. According to severity, it is of 3 types:

- Mild—Factor VIII is > 5 IU/dL (bleeding occurs following major injury or surgery)
- Moderate—Factor VIII is 1 to 5 IU/dL (bleeding occurs following minor injury or surgery)
- Severe—Factor VIII is <1 IU/dL (spontaneous bleeding into the joints, muscles).

Q. What is the **pedigree** of hemophilia?

A. As follows:

1. If father is affected:
   - All daughters are carriers
   - All sons are normal.

2. If mother is carrier:
   - 50% daughters are carriers
   - 50% sons are sufferers.

Note Remember the following points:

- In female carrier—1 son is affected, 1 son in normal, 1 daughter is carrier and 1 daughter is normal.
- In a female carrier, factor VIII is < 50% normal, because of randomized inactivation of one X-chromosome.

Q. Can a **female** be the **sufferer** in hemophilia?

A. Yes, rarely a female can suffer, because of the following reasons:

- If her mother is a carrier and father is a sufferer of hemophilia
- Turner's syndrome (45 XO)
- According to lyoniation theory, there is randomized inactivation of one X chromosome in the developing fetus. Then the number of affected X chromosome may be predominant. Female may be affected, if normal X chromosome is disproportionately inactivated.

Q. How does a patient with hemophilia usually **present**?

A. Depends on whether factor VIII deficiency is mild, moderate or severe.

- Prolonged and persistent bleeding after trauma or injury, tooth extraction
- Sometimes, spontaneous bleeding may occur in severe cases
- Bleeding into the large joints and muscles (psoas and calf muscle) is also common.

Q. What is the common site of **muscular bleeding?**

A. Commonly in calf muscles and psoas.

Q. What happens if the patient has **bleeding into the psoas** muscle?

A. As follows:

- Severe pain in lower abdomen
- Paresthesia in thigh and weakness of quadriceps, due to compression of femoral nerve.

Q. What **investigations** are done in hemophilia?

A. As follows:

- FBC, platelet (usually normal)
- Bleeding time (normal)
- Prothrombin time (normal)
- Clotting time (prolonged)
- APTT (prolonged)
- Factor VIII: C assay (deficient or absent)
- vWF (normal)
- Serum fibrinogen (normal)
- X-ray of involved joint (in hemophilic arthritis).

Note Remember the following:

APTT is prolonged, which is corrected by addition of normal plasma. If not corrected after the addition of normal plasma, more likely there is antibody formation or the presence of anti-phospholipid antibody.

Q. Is **antenatal diagnosis** possible?

A. Yes. Antenatal diagnosis may be done by molecular analysis of fetal tissue obtained by chorionic villus biopsy at 11 to 12 weeks of pregnancy.

Q. How will you **manage hemophilia**?

A. As follows:

1. Management of bleeding episode:
   - Factor VIII concentrate is given by intravenous infusion, twice daily as its half-life is 12 hours and the blood level should be maintained for 3 to 5 days.
   - For minor bleeding, factor VIII level should be raised to 20 to 30 IU/dL. However, desmopressin 0.3 μg/kg 12 hourly infusion over 20 minutes may be given that raise factor VIII.
   - For severe bleeding, factor VIII level should be raised to at least 50 IU/dL. Treatment to be continued for a period of 1 week or more.
   - For major surgery—factor VIII level should be raised to 100 IU/dL preoperatively and maintained above 50 IU/dL until healing. Continuous infusion may be needed. Treatment to be continued for 7 to 10 days.
2. If factor VIII is not available—cryoprecipitate, fresh frozen plasma or fresh blood can be given.
3. To prevent recurrent bleeding into joints and subsequent joint damage—factor VIII infusions should be given regularly thrice a week starting from early childhood (around 2 years of age).
4. Synthetic vasopressin (desmopressin, an analog of vasopressin) is given intravenous, subcutaneous or intranasally. It produces 3 to 5 fold rise in factor VIII:C and is very useful in patient with a baseline level of factor VIII >10 IU/dL. It prevents the complications associated with blood products. It is useful for treating bleeding episodes in mild hemophilia and as prophylaxis before minor surgery, ineffective in severe hemophilia. It is also given for vWD, but not in Christmas disease.

Note Remember the following points:

- 1 unit/kg factor VIII will raise blood level by 2%. So, the dose of factor VIII is calculated as follows:

  FVIII dose = Desired factor VIII level – FVIII baseline level × body weight (kg) × 0.5 unit/kg.
- Previously, factor VIII was prepared from plasma. It is now prepared by recombinant DNA technology (so, there is less risk of transfusion transmitted infection, but more expensive).
- Advice to the patient—trauma should be avoided and precaution should be taken before tooth extraction and surgery. The patient should carry a special medical card in which details of the disease and its treatment must be recorded.

Q. What are the **complications** of hemophilia?

A. As follows:

1. Due to repeated hemorrhage:
   - Arthropathy due to repeated bleeding in joint (e.g. knee, elbow)
   - Atrophy or wasting of muscles secondary to hematoma in muscle
   - Mononeuropathy due to pressure by hematoma
   - Death may occur due to intracerebral hemorrhage.
2. Due to therapy:
   - Infections—Hepatitis A, B, C, D. Also, HIV
   - Factor VIII antibody (up to 30% patients with severe hemophilia).

Note Remember the following points:

- Risk of viral transmission is eliminated because of prior screening of donors
- Infectious agents that can cause Crutzfeldt Jakob disease, may be transmitted by blood and blood products
- All patients should receive vaccination for HAV and HBV
- Use of recombinant factor VIII effectively eliminated transfusion transmitted infection.

Q. If **factor VIII antibody** develops, how can it be suspected and treated?

A. It is suspected if no response to factor VIII in therapeutic dose. APTT is prolonged. In normal hemophilia, APTT is corrected by addition of normal plasma in 1:1 ratio. But if factor VIII antibody develops, APTT is not corrected with normal plasma in this ratio. This case is very difficult to treat. Following options are available:

- High dose and frequent infusion of factor VIII may be given
- Changing the species, such as porcine factor VIII may be used
- Factor IX may be used. It helps bypassing the inhibitors
- Recombinant factor VIIa—helps bypassing the inhibitors.
- Factor eight inhibitor bypassing activity (FEIBA, an activated concentrate of factors II, IX and X), or, prothrombin complex concentrate (PCC) that contains factor VII, IX and X may be used.
- Sometimes, immunosuppressive therapy, such as steroid, azathioprine or cytotoxic drugs may be given
- In long-term, management is to eradicate inhibitory antibody. This can be done by using immune tolerance induction (ITI). Recently, anti-CD20 monoclonal antibody (rituximab) as coadjuvant is promising.

Q. What are the **causes of death**?

A. As follows:

- Bleeding, mainly intracerebral
- HIV related
- Hepatitis due to HCV.

CHRISTMAS DISEASE

It is also called hemophilia B. It is because of deficiency of factor IX. Features are like hemophilia A. It is treated with factor IX concentrate, half-life is 24 hours. Prophylaxis is given twice a week. Desmopressin is ineffective.

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Neurology

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PARKINSONISM

CHIEF COMPLAINTS

- Tremor of the whole body for … months
- Stiffness and difficulty in walking for … months
- Weakness and generalized body ache for … months.

HISTORY

History of present illness: According to the statement of the patient, he was reasonably well … months back. Since then, he has been experiencing tremor of the body. Initially, the tremor was present at the right hand, followed by the left hand, tongue, head and rest of the body. It is present during rest and reduces during any voluntary activity. His wife mentioned that the tremor is absent during sleep. Recently, for … months, the patient feels increasing weakness and stiffness of the whole body, difficulty in walking, performing daily activities like combing, eating, writing, etc. He also complains of generalized persistent bodyache, which is not related to any activity or rest. His bowel and bladder habits are normal. There is no history of head injury, fever, headache, unconsciousness, convulsion or intake of any offending drug.

History of past illness: Nothing significant.

Family history: There is no similar illness in the family.

Personal history: He is a service holder, nonsmoker, nonalcoholic, there is no history of drug abuse.

Drug and treatment history: He gives no history of taking any offending drug related to his illness (e.g. antipsychotics).

GENERAL EXAMINATION

- Titubation of head
- The face is mask-like, expressionless and apathetic (less wrinkling of forehead)
- There is less blinking of the eyes, with staring look (frequency of spontaneous blinking is reduced, called serpentine stare)
- Blepharoclonus (tremor of eyelids, when eyes are gently closed)
- Dribbling of saliva
- No anemia, jaundice, cyanosis, edema, thyromegaly, lymphadenopathy
- Pulse: 72/min
- BP: 125/75 mm Hg
- Temperature: 98.6° F.

SYSTEMIC EXAMINATION

Nervous System

1. Higher psychic (cerebral) functions:
   - The patient is conscious, cooperative and alert
   - Intelligence and memory—intact
   - He looks depressed

- Speech—slow initiation, husky, slurred, indistinct, lacking intonation, low volume and monotonous (or mutism). Palilalia is present (repetition of the end of a word).
- Orientation to time, place, person—intact.

2. Cranial nerves including fundoscopy: Intact.

3. Motor system:
- Muscle tone—lead pipe (better seen in elbow) and cog wheel (better seen in wrist) rigidity are present
- Muscle power—normal
- Reflex—normal (however may be difficult to elicit because of rigidity)
- Plantar response—flexor (may be difficult to elicit)
- Coordination—could not be tested (because of rigidity)
- Gait—flexed and stooped attitude on standing. He has difficulty in starting to walk (freezing). Steps are short, shuffling with paucity of movement, less swinging of the arms, flexed attitude and inability to turn rapidly (fractionated turn).

4. Involuntary movement:
- Resting tremor is present in all the extremities, specially on thumb and fingers (pill-rolling). It disappears or reduces with activity or holding something, or on complete relaxation (better term—"tremor in the position of repose". Ask the patient to keep the arm rested in semiprone position).
- There is titubation of the head.

5. Other findings:
- Glabellar tap (Myerson's sign)—present (repetitive tapping on the forehead above the bridge of the nose, two per second, produces a sustained blink response. In normal person, blinking will stop after three to five blinks. This sign is unreliable).
- There is slow initiation of movement (hypokinesia)—the patient may be unable to perform the act or can do slowly or progressive reduction of amplitude of each movement. Ask the patient to perform the following:
  - Fastening of button
  - Drinking of water from a glass
  - Touching tips of all the fingers with thumb successively or count the number like 1 to 5.
  - Performing rapid fine finger movements like piano playing (it becomes indistinct, slurred and tremulous)
  - Performing two different simultaneous motor acts.
- Handwriting (there is micrographia, handwriting becomes small, tremulous and cramped).

6. Sensory functions: Intact.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 55 years old, service holder, normotensive, nondiabetic, smoker, hailing from …, presented with tremor of the body for … months. Initially, the tremor was present at the right hand, followed by the left hand, tongue, head and rest of the body. It is present during rest and reduces during any voluntary activity. His wife mentioned that the tremor is absent during sleep. Recently, for … months, the patient feels increasing weakness and stiffness of the whole body, difficulty in walking, performing daily activities like combing, eating, writing, etc. He also complains of generalized persistent body ache, which is not related to any activity or rest. His bowel and bladder habits are normal. There is no history of head injury, fever, headache, unconsciousness, convulsion or intake of any offending

drug. There is no similar illness in the family. He was a previous smoker but has stopped smoking about 6 months ago. He gives no history of drug abuse. He gives no history of taking any offending drug related to his illness (e.g. antipsychotics). There is no family history of such illness. He was treated with vitamins by local physicians.

On Examination

General examination (mention as above)

Systemic examination (mention as above).

My diagnosis is Parkinson's disease (paralysis agitans).

Q. What specific **past history** have you taken in this patient?

A. As follows

- History of head injury (punch drunk syndrome)
- Drugs (phenothiazine, butyrophenone, metochlopramide, tetrabenazine, α methyldopa, lithium, valproic acid, fluxetine)
- Any history of fever, convulsion, headache, coma (postencephalitic)
- Jaundice, CLD (in Wilson's disease, occur in early age).
- Any history of headache, vomiting, convulsion (cerebral tumor).

Q. What **investigations** should be done in Parkinsonism?

A. Diagnosis is usually clinical. Investigations are done for specific cases or to exclude other diseases:

1. CT scan or MRI (may be done if pyramidal, cerebellar and autonomic involvement or doubtful diagnosis).
2. In patient < 50 years, screening for Wilson's disease:
   - Serum ceruloplasmin (low)
   - Serum copper (high serum free copper)
   - 24 hours urinary copper (high). Following penicillamine therapy, 24 hours urinary copper > 25 mmol (confirmatory)
   - Liver function tests may be done
   - Liver biopsy with quantitative measurement of copper (less done).

RELATED QUESTIONS AND ANSWERS

Q. What are the **diagnostic criteria** for Parkinsonism?

A. **Triad** of **T**remor at rest (4 to 6 Hz), **R**igidity and **H**ypokinesia (remember the formula **TRH**. According to Brain Bank criteria, postural instability is another criteria).

Q. What is **Parkinsonism?**

A. It is a syndrome consisting of tremor, rigidity, bradykinesia and loss of postural reflexes.

Q. What is **Parkinson's disease?**

A. Parkinson's disease (paralysis agitans) is the primary or idiopathic Parkinsonism. It is a neurodegenerative disorder due to involvement of the basal ganglia, characterized by slowness of movement, rigidity, tremor and loss of postural reflex.

Q. What is **Parkinsonian plus?**

A. It is characterized by features of Parkinsonism with other degenerative disease like progressive supranuclear palsy (Steele-Richardson-Olszeweski syndrome), olivo-ponto-cerebellar degeneration, nigrostriatal degeneration, primary autonomic failure (Shy-Drager syndrome).

Q. Describe the **tremor** in Parkinsonism.

A. Tremor is involuntary, coarse (4 to 6 Hz), present at rest, disappears or reduces during voluntary activity and sleep, and increases with emotion or anxiety. Initially, the tremor is characterized by pill-rolling movement between thumb and index finger, flexion and extension of fingers, abduction and adduction of thumb and pronation and supination of forearm. Later, tremor may affect arms, legs, feet, jaw and tongue. Tremor is absent in one-third cases at presentation and throughout its course in some cases.

Commonly, the patient presents with unilateral resting tremor in hand.

Q. What are the types of **rigidity** in Parkinsonism?

A. Two types:

- Lead pipe—uniform rigidity in flexors and extensors of limbs (better seen in elbow or knee).
- Cog wheel—rigidity is interrupted by tremor (better seen in wrist joint). It is due to exaggerated stretch reflex interrupted by tremor.

Note Remember the following:

Rigidity of the examining limb is increased, with simultaneous active movement of the opposite limb (one type of reinforcement).

Q. What is the difference between **rigidity and spasticity**?

A. As follows:

- Rigidity means increased muscle tone affecting opposing muscle groups equally, which is present throughout the range of passive movement. It may be "lead-pipe" rigidity (uniform and smooth) or "cog-wheel" (intermittent, due to tremor). It is found in extrapyramidal lesion.
- Spasticity (clasp-knife) means increase tone in muscles, which is maximal at the beginning of movement and suddenly decreases as passive movement is continued. It occurs mainly in flexor muscles of the upper limb and extensor muscles of the lower limb (antigravity muscles). It is seen in upper motor neuron lesion.

Q. What are the features of **hysterical rigidity**?

A. In hysterical rigidity, muscle tone increases more and more with increasing maneurve of the affected limb. The more the limbs are moved or examined, the more rigid it gets.

Q. What is **dyskinesia or akinesia**? Describe **dyskinesia or hypokinesia** in Parkinsonism.

A. Dyskinesia is the difficulty in initiating motor activity or poverty or slowing of movement (bradykinesia). In Parkinsonism, it may be:

- Difficulty in initiating movement
- Slowness of movement (bradykinesia). The patient is slow and ineffective in attempt to deliver a quick hard blow, he cannot complete a rapid ballistic movement
- Poverty of movement
- Alternative movement progressively impeded, finally blocked completely
- Difficulty in executing two motor acts simultaneously
- Bradykinesia reflected also by slowness in chewing, limited capacity to make postural adjustment.

Q. Describe the typical **gait** in Parkinsonism.

A. Festinate gait, characterized by:

- Rapid small shuffling step (festination) in order to avoid falling. The patient hardly raises the foot from the ground
- The patient seems to catch up with his own center of gravity (flexed attitude)

- There is less swinging of the arms during walking
- The patient has difficulty in stopping himself
- He has difficulty in rapid turning (fractionated gait) and turns en block
- Obstacles cause the patient to freeze in place.

Q. What are the other **abnormal gaits** in Parkinsonism?

A. As follows (these tests should not be done at the bedside):

- Propulsion—if the patient is pushed from behind, he is unable to stop himself and may fall forward.
- Retropulsion—if the patient is pushed from front, he is unable to stop himself and may fall backward.
- Kinesia paradoxica—the patient is unable to initiate a movement, but once started, can complete the whole act (may run down the stairs, but cannot stop at the bottom) or the patient is unable to initiate a movement, but during emotion or fear (e.g. fire in the house), can perform the movement (even run out from the house).

Q. What are the **reflexes** and **plantar response** in Parkinsonism?

A. All the reflexes and plantar responses are normal. May be difficult to elicit, because of rigidity. Plantar is flexor. It may be extensor if associated with the following disorders -

1. Postencephalitic parkinsonism.
2. Other diseases (called atypical parkinsonian syndrome):
   - Shy-Drager syndrome
   - Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy)
   - Olivopontocerebellar atrophy (OPCA)
   - Corticobasal degeneration (CBD).

Q. What is the **pathological change** in Parkinsonism?

A. In idiopathic Parkinsonism, there is progressive degeneration of the pigmented dopaminergic neurons of substantia nigra and formation of eosinophilic cytoplasmic inclusions in neurons (Lewy bodies, which is the pathological hallmark). Hence, there is deficiency of dopamine (and melanin) with relative increase in cholinergic transmission (imbalance between dopamine and acetylcholine).

Q. What are the **causes** of Parkinsonism?

A. Unknown, multiple factors are responsible:

1. Paralysis agitans (idiopathic, also called Parkinson's disease). It usually occurs in middle aged or elderly
2. Postencephalitic (encephalitis lethargica and Japanese B encephalitis)
3. Drugs: Phenothiazines (chlorpromazine, prochlorperazine), butyrophenones (haloperidol), metoclopramide, sulpiride, cisapride, tetrabenazine and methyldopa
4. Neurosyphilis
5. Poisoning—carbon monoxide, manganese and MPTP (methyl phenyl tetrahydropyridine) may occur in drug addicts
6. Herbicide (paraquat, may be related to MPTP)
7. Trauma (punch-drunk syndrome and repeated head injury)
8. Genetic (Wilson's disease and Huntington's disease)
9. Cerebral tumor (involving basal ganglia)
10. Parkinsonian plus (when associated with features or pathology of othe disease):
    - Shy-Drager syndrome.
    - Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy, characterized by inability of the movement of eye vertically or laterally and dementia)
    - Olivopontocerebellar degeneration

11. Creutzfeldt-Jakob disease
12. Hypoparathyroidism
13. Normal pressure hydrocephalus (triad of urinary incontinence, gait apraxia and dementia)
14. Atherosclerotic Parkinsonism (stepwise progressive broad-based gait and pyramidal signs).

Q. What are the **causes** of Parkinsonism according to **age**?

A. As follows:

1. In elderly, the causes are:
   - Idiopathic or paralytic agitans (the most common cause)
   - Drugs
   - Others—postencephalitic Parkinsonism, neurosyphilis, trauma, cerebral tumor.
2. In young, the causes are:
   - Postencephalitic Parkinsonism
   - Drugs
   - Wilson's disease.

Q. How to **differentiate** between post-encephalitic Parkinsonism and paralytic agitans?

A. As follows:

Criteria	Postencephalitic	Paralytic agitans
1. Age	Any, commonly young	Elderly or late middle age
2. Onset	Sudden	Insidious
3. Previous history	Encephalitis, fever and headache	No particular history
4. Complaints	Mainly rigidity, also impaired higher functions, excess salivation (autonomic features), little or no tremor	Mainly tremor
5. Symmetry	Fairly symmetrical rigidity and hypokinesia	Asymmetrical
6. Eye signs: – Oculogyric crisis – Ophthalmoplegia – Pupil	 Present Present Abnormal (dilated, irregular)	 Absent Absent No abnormality
7. Neurological features: – Dystonia, dementia, chorea, hemiparesis – Rigidity – Tendon reflexes – Plantar response	 Present Usually lead pipe (due to absence of tremor) Brisk Extensor	 Absent Usually cogwheel Normal Flexor
8. Levodopa	Less sensitive	Sensitive
9. Prognosis	Not good	Slowly progressive
10. Lewy body	Absent	Present

Q. What is **oculogyric crisis**?

A. It is an involuntary, sustained upward and outward deviation of the eyes. Causes are:

- Postencephalitic Parkinsonism
- Drugs (commonly phenothiazines)
- Petit mal epilepsy.

Q. What are the **differences** between essential tremor and Parkinsonian tremor?

A. As follows:

Features	Essential tremor	Parkinsonian tremor
1. Stimulus	Occurs with action	Occurs with rest
2. Family H/O tremor	Yes	No
3. Body parts involved	Hands, head	Hands, legs, rarely head
4. Distribution at onset	Bilateral and symmetric	Unilateral and asymmetric
5. Sensitivity to alcohol	Yes	No
6. Course	Stable and slowly progressive	Progressive

Q. What is the **mental status** in a patient with Parkinsonism?

A. As follows:

- Initially, intellect and memory are normal. There may be slowness of thought and memory retrieval (bradyphrenia) and subtle personality changes
- Depression occurs in one-third of the patients
- Global dementia (20%) and psychosis
- Drug treatment may precipitate acute confusion.

Q. What are the **treatment modalities** in Parkinsonism?

A. As follows:

- Treatment of the cause and withdrawal of offending drugs, if any
- Symptomatic treatment of tremor, rigidity and bradykinesia
- Physiotherapy and speech therapy
- Surgical treatment
- Occupational therapy and rehabilitation.

Q. What is the **treatment** of Parkinson's disease?

A. Drug treatment is usually not started in mild case, because of untoward side effects. It should be started when there is significant disability and when the symptoms begin to interfere with work and social life or falling becomes a threat. Combination of levodopa and dopa decarboxylase inhibitor is the treatment of choice. Available combinations are:

- Levodopa and carbidopa (co-careldopa 110 or 275 mg)
- Levodopa and benserazide (co-beneldopa 62.5 mg).

Treatment should be started with lowest possible dose and gradually increased as needed.

- Tremor and rigidity may be controlled by anticholinergic drugs.

General measures:

- Physiotherapy and speech therapy
- Occupational therapy and rehabilitation.

Other measures:

- Cognitive impairment and psychiatric symptoms may be helped by rivastigmine (a selective

serotonin reuptake inhibitory—SSRI are drugs of choice for depression. These drugs may aggravate Parkinsonian symptoms. Trazodone is helpful in treating depression and insomnia).
- For psychosis, confusion or hallucination—atypical antipsychotic can be given.

Q. What is the **role of surgery** in Parkinsonism?

A. Surgery is rarely done because medical treatment is available. Options are:
- Stereotactic thalamotomy (ventrolateral nucleus of thalamus) or pallidotomy for tremor contralateral to the side of the body affected
- Deep brain stimulation—high frequency thalamic stimulation may be helpful in suppressing tremor. Also, chronic bilateral stimulation of subthalamic nuclei or globus pallidus may be beneficial
- Foetal midbrain or adrenal tissue implantation in basal ganglia (not much beneficial).

Q. What are **stages** of Parkinsonism?

A. As follows:
- Stage I—Unilateral involvement (hemiplegic Parkinsonism)
- Stage II—Bilateral involvement, but no postural abnormality
- Stage III—Bilateral involvement with mild postural abnormality
- Stage IV—Stage 3 plus severe postural abnormality requiring substantial help
- Stage V—Severe, fully developed disease. The patient is restricted to bed and wheelchair.

A BRIEF NOTE ON DRUGS USED IN PARKINSONISM

Levodopa:

- It crosses blood brain barrier and is decarboxylated into dopamine.
- It is given with peripheral decarboxylase inhibitor (e.g. carbidopa, benserazide in 4:1 ratio) to reduce its peripheral metabolism.
- Dose—50 mg 12 or 8 hourly and increased as needed upto 1000 mg/day.
- In the elderly, L-dopa is the first line of treatment as it has the best therapeutic index.
- Levodopa is contraindicated in psychosis, narrow angle glaucoma and malignant melanoma or PUD (as it may exacerbate these diseases).
- It should not be given in a patient taking MAO-A inhibitor or within 2 weeks of withdrawal, because of hypertensive crisis (cheese effect).
- Side effects—nausea, vomiting, postural hypotension, orofacial dyskinesia, limb and axial dystonia, occasionally depression, hallucination and delusion.
- After 3 to 5 years of levodopa therapy, there may be fluctuating response to levodopa in about one-third to one half of the patients. These include:
  i. **End of dose deterioration** (wearing off effect): Due to progression of the disease and loss of capacity to store dopamine, duration of action of a dose of levodopa becomes progressively shorter. As a result, the patient complains of freezing and rigidity before the next dose of levodopa. This may be managed by dividing levodopa into smaller, but for frequent doses or by using slow-release preparations or adding dopamine agonist or adding amantadine.
  ii. **On-off phenomenon**: After prolonged use, the drug may become less effective. There is sudden, unpredictable change in response, in which periods of severe Parkinsonism (freezing and immobility—the off period), alternate with periods of dopamine induced dyskinesias, agitation, chorea and dystonic movements (the on period). Adjust L-dopa dose or interdose interval or add COMT inhibitor or add dopamine agonist.

Anticholinergics:

- Trihexyphenidyl, benzhexol, orphenadrine, benztropine, phenoxene, biperiden, cycrimine, procyclidine, etc
- Useful in controlling tremor and rigidity, not helpful for bradykinesia
- Adverse effect—urinary retention, worsening of glaucoma, confusion, dry mouth, constipation
- Should be avoided in elderly patient
- Contraindicated in prostatic hyperplasia, narrow angle glaucoma, obstructive gastrointestinal disease.

Dopamine receptor agonists:

- These may be ergot derivatives (bromocriptine, pergolide, lisuride) or non-ergot (ropinirole, pramipexole)
- Bromocriptine, cabergoline, lisuride, pergolide, ropinirole, pramipexole, etc. are given orally. Rotigotine can be administered as a transdermal patch. These are alternative or addition to levodopa therapy
- Side effects are anorexia, nausea, vomiting, hallucination, confusion, orthostatic hypotension, excessive or abrupt sleepiness, leg edema.

MAO-B inhibitor:

- Selegiline is a MAO-B inhibitor and used as an adjuvant to levodopa therapy, it prevents the breakdown of dopamine. Dose is 5 to 10 mg in the morning. Recent evidences show that it can slow down degeneration in substantia nigra and is recommended to be used in all patients from early stages of the disease. Tyramine rich food should be avoided when these are used, because of the possibility of hypertensive crisis (cheese reaction)
- Rasagiline, a selective MAO-B inhibitor, 1 mg daily in the morning, may be used as an adjuvant therapy in patient with response fluctuation to levodopa.

Catechol-O-methyltransferase (COMT) inhibitors:

- Tolcapone and entacapone are COMT inhibitors, used with levodopa.
- These enhance the benefits of levodopa by reducing the conversion of levodopa to 3-O-methyldopa, which competes with levodopa for an active carrier mechanism. This increases the availability of levodopa in brain. They are useful in patient with fluctuating response to levodopa.

Amantadine:

- Potentiates endogenous dopamine (presynaptic agonist) and has mild antiparkinsonian effect
- Dose—100 mg 8 or 12 hourly
- Useful early in the disease or in conjunction with levodopa replacement
- Side effects—postural hypotension, confusion, peripheral edema, livedo reticularis, seizure, CCF, hallucination, insomnia, prostatic outlet obstruction.

Q. What are the **extra-pyramidal effects** of different antipsychotic drugs?

A. Phenothiazine, butyrophenones, metoclopramide, etc. can produce multiple abnormal movements. These may be:

- Parkinsonism (tremor is less and responds to anticholinergic drugs than L-dopa)
- Dystonia (commonly by prochlorperazine and metoclopramide)
- Akathisia (it is the uncontrolled restlessness with repetitive and irresistible need to move)
- Tardive dyskinesia—characterized by orofacial dyskinesia including lip smacking, chewing,

pouting and grimacing. It is usually due to use of phenothiazines and butyrophenones for at least 6 months. May be worse or may persist after the withdrawal of drug. Tetrabenazine may help

❖ Chorea.

Q. What are the **types** of dyskinesia or movement disorder?

A. As follows:

1. Hypokinetic—PD, PD plus
2. Hyperkinetic:
   a. Rhythmic: Tremor
   b. Non-rhythmic:
      - Chorea (lesion in caudate nucleus)
      - Athetosis (lesion in putamen)
      - Hemiballismus (lesion in subthalamic nucleus)
      - Myoclonus (lesion in multiple areas of brain)
      - Dystonia (site of lesion unknown)
      - Tics (site of lesion unknown).

MOTOR NEURON DISEASE

CHIEF COMPLAINTS

- Weakness and inability to walk for … months
- Weight loss and wasting of the limbs for … months
- Occasional twitching of the muscles of the limbs for … months.

HISTORY

History of present illness: According to the statement of the patient, he was alright … months back. Since then, he has been suffering from generalized weakness, which is progressively increasing and for the last few weeks, he is unable to walk without the help of others. The patient also complains of weight loss which is not associated with excessive sweating, polyuria, excessive thirst, cough or diarrhea. For the last … months, he noticed progressive wasting of the lower limbs initially, followed by muscles of the hands and forearms. The patient also experienced occasional spontaneous twitching movement of different parts of the body associated with muscle cramps. His bowel and bladder habits are normal. He denies any history of difficulty in deglutition, nasal regurgitation. There is no loss of sensation in any part of the body.

History of past illness

Socioeconomic history

Family history

Drug and treatment history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient is emaciated and ill looking
- No anemia, jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- Pulse: 90/min
- BP: 150/80 mm Hg.

SYSTEMIC EXAMINATION

Nervous System

1. Higher psychic functions: Normal (or there may be emotional lability)
2. Cranial nerves: Intact
3. Motor system:
   - There is wasting of all muscles of lower limbs, both hands and forearm
   - Muscle tone—increased in both lower limbs, normal in the upper limbs
   - Muscle power is diminished in both lower limbs (grade 4/5), also in upper limbs (grade 3/5). All the small muscles of hands are weak
   - Reflexes:

Jerks	Biceps	Triceps	Supinator	Knee	Ankle	Plantar
Right	Diminished	Diminished	Diminished	Exaggerated	Exaggerated	Extensor
Left	Diminished	Diminished	Diminished	Exaggerated	Exaggerated	Extensor

- There is patellar and ankle clonus (mention, if any)
- Coordination is impaired due to weakness of the muscle.

4. Involuntary movement: Multiple fasciculations in both thigh muscles and few in upper limb muscles
5. Sensory: Intact
6. Gait: Spastic gait.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 45 years old, businessman, normotensive, nondiabetic, nonsmoker, hailing from …, presented with generalized weakness for … months, which is progressively increasing and for the last few weeks, he is unable to walk without the help of others. He also complains of weight loss which is not associated with excessive sweating, polyuria, excessive thirst, cough or diarrhea. For the last … months, he noticed progressive wasting of the lower limbs initially, followed by muscles of the hands and forearms. The patient also experienced occasional spontaneous twitching movement of different parts of the body associated with muscle cramps. His bowel and bladder habits are normal. He denies any history of difficulty in deglutition, nasal regurgitation. There is no loss of sensation in any part of the body. He was treated with multiple vitamins by local physicians. There is no history of such illness in his family.

On Examination
General examination (mention as above).
Systemic examination (mention as above).

My diagnosis is motor neuron disease (MND), more likely amyotrophic lateral sclerosis.

Q. Why it is **MND?**

A. Because, there is wasting of muscles, no sensory loss, but exaggerated reflex. Also, fasiculations are present.

Note Remember, if any patient presents with:

- Wasting (and weakness) of muscles
- But exaggerated reflex
- No sensory loss (but fasciculation is present).

Diagnosis should be motor neuron disease, until proved otherwise.

Q. Why **amytrophic lateral sclerosis?**

A. Because, there is lower motor neuron lesion in the upper limb and upper motor neuron lesion in the lower limb (combined UMN and LMN lesion indicates amyotrophic lateral sclerosis. Amyotrophy means muscle atrophy and lateral sclerosis means lesion in lateral corticospinal tract).

Q. Mention **one common differential diagnosis** to be excluded in such case.

A. Cervical cord compression involving C5 and C6 may present with lower motor neuron lesion in the upper limb and upper motor neuron lesion in the lower limb. In such case, MRI of cervical spine should be done.

Q. What are the **differential diagnoses?**

A. As follows:

1. Diabetes mellitus
2. Syphilitic amyotrophy or syphilitic cervical pachymeningitis
3. Paraneoplastic syndrome (commonly due to bronchial carcinoma)
4. Sarcoidosis
5. Spinal diseases:
   - Cervical cord compression
   - CASMA (chronic asymmetrical spinal muscular atrophy)
   - Old poliomyelitis (confuses with progressive muscular atrophy)
   - Spinal muscular atrophy of juvenile onset type 3 (onset in childhood, mild form, affects mostly proximal muscles)
   - Motor neuropathy due to any cause (confuses with progressive muscular atrophy).

Q. Could it be **syringomyelia**?

A. Unlikely, as in syringomyelia there is dissociated sensory loss.

Q. What **investigations** should be done in this case?

A. No specific test, diagnosis is usually clinical. Investigations are done to exclude other diseases:

- Blood sugar (to exclude diabetic amyotrophy)
- VDRL or TPHA (to exclude neurosyphilis)
- Chest X-ray (to exclude bronchial carcinoma)
- X-ray of the cervical spine
- Ultrasonogram of whole abdomen (to see any neoplasm)
- EMG (to confirm fasciculation and denervation)
- NCV (normal motor and sensory conduction)
- Lumbar puncture and CSF study (no abnormality, only slightly raised protein)
- CT or MRI (brain and spinal cord).

Note There are certain '*No's* in MND:

- No sphincter disturbance (rarely involved in late case)
- No sensory involvement
- No loss of awareness till death
- No dementia
- No ocular involvement
- No cerebellar or extrapyramidal lesion
- No abnormality of CSF usually.

RELATED QUESTIONS AND ANSWERS

Q. What is **MND?** What are the **causes** of MND?

A. It is a progressive disease of unknown cause, characterized by the degeneration of motor neurons in the spinal cord, cranial nerve nuclei and pyramidal neurons in the motor cortex.

The MND is common in middle aged and elderly, rare before 30 years of age. Male commonly affected than female (pseudobulbar palsy is more in female). There is no remission, and the disease is fatal within 3 to 5 years. Young patients and those with bulbar symptoms show rapid progression.

Causes are unknown, possible factors are:
- Familial—5 to 10% of the cases, may be inherited as autosomal dominant
- May follow viral infection, trauma, exposure to toxin and electric shock
- Glutamate toxicity has been implicated as a factor in amyotrophic lateral sclerosis (ALS).

Q. What is the **pathology** of MND?

A. Degeneration of Betz cells, pyramidal tract, cranial nerve nuclei and anterior horn cells. Both UMN and LMN may be involved, but no sensory involvement.

Q. What are the **types** of MND?

A. According to the site of lesion:

1. Spinal cord lesion:
   - Progressive muscular atrophy (PMA)—LMN lesion
   - Amyotrophic lateral sclerosis (ALS)—combined UMN and LMN (LMN lesion in upper limbs and UMN lesion in lower limbs)
   - Primary lateral sclerosis (PLS)—pure UMN lesion (rare).
2. Cerebral lesion:
   - Progressive bulbar palsy—medullary lesion.
   - Pseudobulbar palsy—cortical lesion.

According to type of lesion:

1. Pure UMN lesion—PLS, pseudobulbar palsy
2. Pure LMN lesion—PMA, bulbar palsy
3. Mixed lesion—ALS.

FEATURES AND DIAGNOSIS OF INDIVIDUAL MND

Progressive muscular atrophy:

- Weakness, wasting and fasciculation of distal limb muscles, usually starting in small muscles of one or both hands
- Tendon reflexes are lost (due to involvement of anterior horn cell).

Amyotrophic lateral sclerosis:

- Weakness, wasting, fasciculation and loss of all reflexes (LMN lesion) in upper limb **plus** spastic weakness with exaggerated reflexes and extensor plantar response in lower limb (UMN lesion). In advanced stage, there may be generalized hyperreflexia.
- Bulbar and pseudobulbar palsy may follow eventually.

Primary lateral sclerosis:

- Only UMN lesion (upper limb and lower limb)
- Progressive tetraparesis with terminal pseudobulbar palsy occur.

Progressive bulbar palsy:

- Presents with **3 "D"s—d**ysarthria, **d**ysphonia and **d**ysphagia. There is nasal regurgitation, dribbling of saliva
- Speech is nasal, indistinct and slurred
- Tongue—wasted, wrinkled and fasciculating
- There is palatal palsy.

- Gag reflex is absent
- Site of lesion: Nucleus of lower cranial nerves in medulla (IX, X, XI and XII). Lesion is bilateral and LMN type.
- Common causes:
  - Motor neuron disease
  - Guillain-Barré syndrome
  - Syringobulbia
  - Brainstem infarction
  - Poliomyelitis
  - Neurosyphilis
  - Neurosarcoid.

Pseudobulbar palsy:

- This is more common in women
- Speech: Nasal, slurred, indistinct and high pitched (so called **Donald Duck** or **hot potato** dysarthria due to tight immobile tongue)
- Tongue: Small and tight, spastic, unable to protrude, but no wasting or fasciculation
- Jaw jerk is exaggerated
- Palatal movement is absent
- Gag reflex is present
- The patient is emotionally labile (crying and laughing)
- Site of lesion: Bilateral UMN lesion (supranuclear) involving the pyramidal tract (supranuclear lesion of lower cranial nerves: IX, X, XI, XII)
- Causes:
  - Bilateral repeated CVA involving internal capsule (multi-infarct dementia)
  - Demyelinating disease (multiple sclerosis)
  - Motor neuron disease.

Q. What are the **differences** between bulbar and pseudobulbar palsy?

A. As follows:

Criteria	Bulbar palsy	Pseudobulbar palsy
1. Type of lesion	LMN	UMN
2. Site of lesion	Medulla	Bilateral, internal capsule
3. Speech	Nasal	Slow, slurred and indistinct
4. Nasal regurgitation	Present	Absent
5. Tongue	Wasted, fasciculation	Small, stiff or spastic
6. Jaw jerk	Absent	Brisk
7. Emotion	Normal	Labile

Q. How to **treat** MND?

A. As follows:

1. No curative treatment
2. Supportive treatment:
   - Physical rehabilitation
   - Psychological support

- Occupational rehabilitation
- Nutritional care—change the form and texture of the food, high calorie food supplement, enteral feeding, PEG (percutaneous endoscopic gastrostomy)
- Speech and communication therapy
- Respiratory therapy—NIPPV
- Home and hospice care, end of life palliative care.

3. Symptomatic treatment:
   - Fatigue—pyridostigmine, amantadine
   - Depression—SSRI, venlafaxine, amantadine
   - Emotional lability—same
   - Cramps—quinine sulfate, vitamin E, clonazepam
   - Fasciculation—carbamazepine
   - Spasticity—baclofen, tizanidine
   - Sialorrhoea—hyoscyamine sulfate, scopolamine patch
   - Joint pain—analgesic, such as NSAIDs
   - Insomnia—zolpidem tartrate
   - Respiratory failure—bronchodilators.
4. Neuroprotective agents: Riluzole, IGF-1, ASO, vitamin E, Coenzyme Q-10, neuroprotective factors. Riluzole is a glutamate antagonist, may retard progression and prolong the survival.

Q. What is the **prognosis** of MND?

A. The MND is a progressive disorder and remission is unknown. It is usually fatal within 3 to 5 years. Younger patient with early bulbar syndrome tend to show a more rapid course. Prognosis is relatively better in progressive lateral sclerosis and progressive muscular atrophy.

Cause of death—bronchopneumonia, respiratory failure and complication of immobility.

Q. What are the causes of **wasting of the small muscles of the hand**?

A. As follows:

- MND
- Syringomyelia
- Charcot Marie Tooth disease
- Cervical spondylosis
- Cervical rib
- Pancoast's tumor
- Following arthritis
- Peripheral nerve lesion (peripheral neuropathy or combined ulnar and medial nerve lesion)
- Myopathy (dystrophia myotonica).

Q. What is the **difference** between fasciculation and fibrillation of muscle?

A. As follows:

- Fasciculation—contraction of groups of muscles. It is visible.
- Fibrillation—contraction of single muscle fibre or unit. It is not visible. Diagnosed by EMG.

Q. What is **fasciculation?** What are the **causes**? What is the **mechanism**?

A. Random spontaneous twitching of a group of muscle fibers or a motor unit that produce movement of the overlying skin or mucous membrane or digits. Fasciculation may be coarse or fine, usually present at rest, but not during voluntary movement. It is usually spontaneous, may be elicited by tapping with finger or hammer over the muscle (this procedure is controversial, as it is not accepted by some neurologists, because it should be spontaneous). If fasciculation is present with weakness and wasting, it indicates LMN lesion.

Mechanism of fasciculation:

It is due to spontaneous firing of surviving axons that strive to innervate the muscle fibers, which have lost their nerve supply.

Causes of fasciculation:

1. Neurogenic:
   - MND
   - Charcot-Marie-Tooth disease
   - Spinal muscular atrophy
   - Radiculopathy (cervical spondylosis, cervical rib)
   - Syringomyelia
   - Peripheral neuropathy
   - CJD
   - Acute stage of poliomyelitis (rarely in old polio)
   - Syphilitic amyotrophy
   - Neuralgic amyotrophy.
2. Metabolic:
   - Tetany
   - Thyrotoxic myopathy
   - Anticholinergic drugs
   - OPC poisoning.
3. Normal:
   - Benign fasciculations (in anxiety or tension. It is usually found around the shoulder joint)
   - After exercise in fit adults
   - After tensilon test
   - Muscle cramps.

Q. What are the **neurological non-metastatic syndromes** of malignancy?

A. As follows:

- Motor neuron disease
- Sensory neuropathy
- Mononeuritis multiplex
- Cranial polyneuropathy
- Eaton-Lambert syndrome
- Spastic paraparesis
- Cerebellar syndrome
- Dementia and encephalopathy
- Progressive multifocal leukoencephalopathy.

Cause of neurological non-metastatic syndromes is unknown. It may precede the clinical manifestation of malignancy. Usually, it is associated with small cell carcinoma of the lung and lymphoma.

Neuromuscular paraneoplastic syndrome (according to the site of lesion):

- **Brain:** Progressive cerebellar degeneration, dementia, myoclonus-opsoclonus
- **Brainstem:** Limbic encephalitis
- **Cranial nerves:** optic neuritis, retinal degeneration or retinopathy
- **Spinal cord:** Myelitis, MND like picture

- **Peripheral nerves:** Subacute and chronic sensorimotor neuropathy, subacute motor neuropathy, pure sensory neuropathy, autonomic neuropathy, GBS like syndrome, brachial neuritis.
- **Neuromuscular:** Lambert Eaton myasthenic syndrome.
- **Muscular:** Dystonia/myotonia, acute necrotising myopathy, stiff-person syndrome, cachexic myopathy, carcinoid myopathy.

Importance of neuromuscular PNS:

- Symptoms may appear quite ahead before the presentation of occult malignancy
- Symptoms may be so severe that may lead to death of the patient
- Symptoms may be confused with metastatic disease of the tumor
- At least three-fourth of the PNS is irreversible and fatal
- Accompanied by various antibodies that may help in the diagnosis of the condition.

MULTIPLE SCLEROSIS

CHIEF COMPLAINTS

- Weakness for … months
- Inability to walk for … months
- Weight loss for … months
- Incontinence of urine and constipation for … months.

HISTORY

History of present illness: According to the statement of the patient, she was alright … months back. Since then, she has been suffering from generalized weakness which is deteriorating progressively. For last … months, she is so weak that she cannot walk even for a short distance without the help of others. The patient also complains of substantial weight loss for the last … months. It is not associated with excessive sweating, polyuria, excessive thirst, cough or diarrhea. For the last … months, he also complains of urinary incontinence during both day and night, which is not associated with pain, burning sensation, frequency of micturition or hematuria. She also complains of constipation, but there is no history of blurring of vision, vertigo, convulsion or facial pain. She denies any history of fever, headache or trauma.

History of past illness: She had a similar attack 1 year back that improved after taking some drugs prescribed by local doctors, the name of which she cannot mention.

Socioeconomic history: High (or upper middle) class.

Family history

Personal history

Drug and treatment history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient looks ill, apathetic and emaciated
- No anemia, jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- Pulse: 74/min
- BP: 115/70 mm Hg.

Nervous System

1. Higher cerebral functions: Normal. Speech is dysarthric and scanning.
2. Cranial nerves:
   - First—intact
   - Fundoscopic findings—temporal pallor of the optic disc in the right eye, left eye is normal
   - Third, fourth and sixth—there is nystagmus in right eye on lateral movement and failure of adduction of left eye (internuclear ophthalmoplegia). Diplopia may be present (mention if any)
   - Rest of the cranial nerves are normal.

3. **Motor system:**
   - Muscle power is diminished, grade 4/5 in the lower limbs, normal in the upper limbs
   - Muscle tone is increased in lower limbs
   - Reflexes:

Jerks	Biceps	Triceps	Supinator	Knee	Ankle	Plantar
Right	Normal	Normal	Normal	Exaggerated	Exaggerated	Extensor
Left	Normal	Normal	Normal	Exaggerated	Exaggerated	Extensor

   - Patellar and ankle clonus—present in both lower limbs
   - Abdominal reflex—lost
   - Coordination—impaired in both lower limbs (due to weakness)
   - Gait—reeling or drunken gait.
4. **Sensory system:**
   - Loss of vibration, position sense and two point discrimination in the right lower limb
   - Other modalities of sensation are normal.
5. **Involuntary movement:** Absent.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mrs …, 52 years old, housewife, normotensive, nondiabetic, nonsmoker, hailing from …, presented with generalized weakness for … months, which is deteriorating progressively. For last … months, she is so weak that she cannot walk even for a short distance without the help of others. The patient also complains of substantial weight loss for the last … months. It is not associated with excessive sweating, polyuria, excessive thirst, cough or diarrhea. For the last … months, the patient also complains of urinary incontinence during both day and night, which is not associated with pain, burning sensation, frequency of micturition or hematuria. She also complains of constipation, but there is no history of blurring of vision, vertigo, convulsion or facial pain. She denies any history of fever, headache or trauma. She had a similar attack one year back that improved after taking some drugs prescribed by local doctors, the name of which she cannot mention. There is no history of such illness in her family. She was treated with vitamins by local physicians.

On examination
General examination (mention as above).
Systemic examination (mention as above).

My diagnosis is demyelinating disease (multiple sclerosis).

Q. Why is it **multiple sclerosis?**

A. From history, she has history of recurrent neurological deficits involving both lower limbs along with incontinence and constipation. On examination, there are scanning speech, internuclear ophthalmoplegia, nystagmus, upper motor neuron lesion in lower limbs, cerebellar gait, ataxia, and temporal pallor of the optic disc in the right eye.

Q. Why not **spinal cord compression?**

A. Because onset over days or weeks, no radicular pain, no history of trauma or vertebral collapse. There is no upper level of sensory loss.

Also internuclear ophthalmoplegia, nystagmus, cerebellar sign's and optic neuritis are against spinal cord compression.

Q. What are the **differential diagnoses?**

A. As follows:

- Spinal cord compression
- Subacute combined degeneration of spinal cord (SCD)
- Neurosyphilis
- Adrenoleukodystrophy
- Recurrent attack of myelitis (see below).

Q. What are the causes of **recurrent attack of myelitis?**

A. As follows:

- Central nervous system sarcoidosis (neurosarcoid)
- Systemic lupus erythematosus (SLE)
- Antiphospholipid antibody syndrome
- Behcet's syndrome
- Sjogren syndrome
- Mixed connective tissue disease
- Spinal AVM
- Dural and cord vascular fistula.

Q. What **investigations** should be done in multiple sclerosis?

A. As follows:

1. MRI of brain and spinal cord—investigation of choice (positive in 95% cases). MRI shows multiple plaques, hyperintense in T_2W and FLAIR, mainly in the periventricular region, corpus callosum, cerebellar peduncles, juxtracortical posterior fossa, brainstem and subpial region of spinal cord. CT scan is not sensitive.
2. Lumbar puncture and CSF study—there is slight increase in lymphocyte, increase in total protein (in 40% cases), and oligoclonal band (in 70 to 90% cases, mainly IgG on electrophoresis).
3. Evoked potential—mainly VEP (visual evoked potential, usually delayed, if there is optic nerve involvement).
4. To exclude other conditions:
   - Chest X-ray (to exclude bronchial carcinoma)
   - X-ray of spine (to exclude cord compression)
   - Serum angiotensin converting enzyme (to exclude sarcoidosis)
   - Serum B_{12} (to exclude subacute combined degeneration of spinal cord)
   - ANA (to exclude SLE)
   - Antiphospholipid antibodies.

RELATED QUESTIONS AND ANSWERS

Q. What is **MS?** What is the **natural history** of the disease?

A. It is a chronic, inflammatory demyelinatig disorder of CNS characterized by multiple plaques of demyelination within the brain and spinal cord, gliosis and varying degree of inflammation. Usually there is relative preservation of axons.

Natural history is extremely variable—may be acute, subacute, insidious, relapsing and remitting, chronic progressive, spontaneous recovery, rapidly progressive and secondarily progressive.

It is also called disseminated sclerosis, as the plaques are **disseminated both in time and space.** Presence of two neurological lesions in anatomically unrelated sites or at different times indicates multiple sclerosis.

Q. What are the **causes** of MS?

A. Unknown, the following factors may be associated:

- Environmental factors—more in temperate zone, and rare in tropical country. Greater among rural than urban dwellers
- More frequent in the higher socioeconomic group
- Genetic—ten times more in first degree relative
- Immunological—there is increase in activated T-lymphocyte in CSF, increase in immunoglobulin in CNS and increase in antibody to some virus (measles)
- Diet—more in those who eat animal fat
- HLA association—DR_2, DR_3, B_7, A_3

Q. What are the **presentations** of MS?

A. Twice more common in females. Age of onset is 20 to 45 years. Before puberty and after 60 years, it is rare. The patient usually presents with:

- Weakness of one or more limbs
- Optic neuritis (the patient complains of blurring of vision)
- Features of spastic paraplegia (confused with spinal cord compression)
- Features of cerebellar signs (ataxia and tremor, etc.)
- Features of brainstem dysfunction (vertigo, diplopia, nystagmus, facial numbness or weakness, dysarthria, dysphagia and pyramidal signs in limbs)
- Bladder dysfunction (incontinence, dribbling and hesitancy)
- Sensory disturbance—tingling of the extremities and light banding sensation around the trunk or limbs (due to posterior column involvement)
- Others (rarely)—epilepsy, trigeminal neuralgia, facial palsy (may be recurrent), 6th nerve palsy, tonic spasm or brief spasm of limbs, dementia, neuropsychiatric dysfunction, depression
- Euphoria despite disability.

Common mode of onset:

1. Optic neuritis (25%)
2. Transverse myelitis (like spinal cord compression)
3. Cerebellar ataxia
4. Various brainstem syndromes—vertigo, facial pain or numbness, dysarthria, diplopia.

To remember the signs and symptoms of MS, remember the mnemonic—**WATSON.**

- **W** – **W**eakness
- **A** – **A**taxia (cerebellar)
- **T** – **T**remor (cerebellar)
- **S** – **S**peech (scanning)
- **O** – **O**ptic neuritis
- **N** – **N**ystagmus.

Q. Which **reflex** is lost early?

A. Abdominal reflex.

Q. What is **triad of Steinberg?**

A. Urinary incontinence, impotence and constipation.

Q. What are the **clinical courses (or types)** of MS?

A. As follows:

- Relapsing and remitting MS (80 to 90%): The patient suffers from episodes of acute worsening with recovery and remains stable between relapses.
- Primary progressive MS (10 to 20%): Gradual neurological deterioration from the onset. It usually begins after 40 years (late onset).
- Secondary progressive MS: Some cases of relapsing and remitting course show gradual neurological deterioration. There may be superimposed acute relapses.
- Fulminating MS (< 10%).

Q. What are **sites of involvement** in MS?

A. As follows:

- Optic nerve
- Brainstem and its cerebellar connection
- Spinal cord (posterior column and corticospinal tract)
- Cerebral white matter particularly periventricular region.

Q. What are the **prognostic factors** in MS?

A. As follows:

1. Good prognostic factors:
   - Early age of onset
   - Relapsing and remitting form of disease
   - Visual or sensory symptoms alone at presentation
   - Minimum neurological impairment 5 years after onset
   - More benign course in women than in men
   - Little residual disability 5 years after onset.
2. Poor prognostic factors:
   - Old age > 40 years
   - Frequent relapse in first 2 years
   - Short interval between first 2 relapses
   - Pyramidal, brainstem and cerebellar symptoms
   - Primary progressive disease
   - Poor recovery from relapse
   - MRI shows many lesions.

Q. What are the **features** of end-stage MS?

A. In end-stage disease, the patient is severely disabled with spastic paraplegia, tetraplegia, ataxia, optic atrophy with blindness, nystagmus, pseudobulbar palsy, urinary incontinence, brainstem dysfunction and dementia.

Q. What is **Uhthoff's** phenomenon?

A. Exaggeration of symptoms after raised body temperature or hot bath is called Uhthoff's phenomenon. The patient feels extreme weakness or transient blurring of vision (minutes) after hot bath. It is due to the slowing of central conduction by increased body temperature.

Q. What happens during **pregnancy** in multiple sclerosis?

A. Mild protective effect may be seen during pregnancy. However, exaggeration may occur in puerperium.

Note Remember the following points in multiple sclerosis:

- Common in women, 20 to 40 years of age (rare before puberty and after 60 years, F: M = 2:1)
- It is called disseminated sclerosis, as it is **disseminated in time and place**
- Presence of two neurological lesions in anatomically unrelated sites or at different times indicates MS
- Patient may complain of blurring or loss of vision. Using fundoscopy nothing is seen (if "doctor sees nothing, patient sees nothing" this is due to retrobulbar neuritis)
- Peripheral nervous system is spared, only CNS involvement
- Causes of death are renal failure and bronchopneumonia.

Q. How to **treat** MS?

A. As follows:

1. During acute attack:
- Intravenous (IV) methylprednisolone—1 g for 3 days or oral 500 mg for 5 days. It shortens the duration of relapse but does not affect the long-term outcome. It is followed by oral prednisolone 40 mg daily for 10 days, then 20 mg for 2 days, then 10 mg for 2 days
- Or, high dose prednisolone—40 to 60 mg daily for 10 days, then taper over 2 days (it has no role for long-term use for prevention)
- Plasmapheresis is sometimes helpful in patient with severe relapse and unresponsive to corticosteroid.

2. To prevent relapse (disease-modifying drugs may be given):
- Immunosuppressive drug—azathioprine may be helpful (cyclophosphamide sometimes helpful in aggressive disease, not recommended for widespread use). Mitoxantrone may be helpful
- Subcutaneous or intramuscular β interferon (1a or 1b) reduces the number of relapse (30%)
- Glatiramer acetate has similar effect. It has immunomodulatory effect
- Monoclonal antibody to beta-integrins (natalizumab), or to lymphocyte epitopes (campath-1H), or alemtuzumab may be helpful in severely affected patient
- IV immunoglobulin may be helpful in aggressive cases.

3. Other supportive treatment for complication and disability:
- For incontinence—intermittent self catheterization, drugs like oxybutynin, tolterodine, etc.
- Urgency or frequency – intermittent self catheterization is advised if post-micturition residual urine is > 100 mL. If < 100 mL, then oxybutynin or tolterodine may be given
- For spasticity—physiotherapy and drugs like baclofen (oral or intrathecal), tizanidine, benzodiazepine or dantrolene may be used. Local intramuscular injection of botulinum toxin or chemical neuronectomy are other options. Cannabis extracts and synthetic cannabinoids are also used
- For dysesthesia—carbamazepine, gabapentin, phenytoin or amitriptyline may be helpful
- For ataxia—INH or clonazepam
- For fatigue—amantadine, modafinil or amitriptyline
- For impotence—sildenafil may be used
- Control of infection
- Prevention of pressure sore
- Rehabilitation.

Q. What is the **role of steroid** in MS?

A. In MS with optic neuritis, high dose intravenous mythylprednisolone for 3 days followed by short course of prednisone may be given. It reduces the rate of relapse of MS over 2 years.

Q. What is the **role of exercise** in MS?

A. The patient should be active during remission and avoid excessive physical exercise during relapses.

Q. What is **Lhermitte's sign**?

A. When the neck is flexed, there is tingling or electric shock like sensation or funny sensation, which passes down in the upper limb, trunk and perhaps lower limbs called Lhermitte's sign (also called barber's chair sign). It indicates the disease is near the dorsal column nuclei of higher cervical cord (indicates cervical cord compression). Causes are:

- MS (the most common cause, especially in acute exacerbation)
- Cervical spondylosis
- Cervical cord compression (by tumor)
- Subacute combined degeneration
- Radiation myelopathy
- Cervical spondylotic myelopathy.

Note

A similar sensation provoked by neck extension may occur, called **reverse Lhermitte's sign**. It strongly suggests cervical spondylosis.

Q. What is the **role of MRI**?

A. The MRI is the single most investigation to confirm the diagnosis of MS, positive in 80% cases. It shows hyperintense focal periventricular white matter lesions in T_2 weighted images. Although these are typical, but not pathognomonic and may be found in small infarcts, disseminated metastases, moya-moya disease and inflammatory diseases.

MRI in MS is helpful for the following:

1. Reveals asymptomatic plaques in cerebrum, brainstem, optic nerves and spinal cord.
2. MS plaques are hyperintence on T_2W and even more strikingly obvious on fluid attenuated inversion recovery (FLAIR).
3. On T_2W, several asymmetrical, well demarcated lesions immediately adjacent to ventricular surface (periventricular lesion) usually denotes MS. Especially diagnostic are oval or linear regions of demyelination oriented perpendicularly to the ventricular surface. When viewed on sagittal images, they extend outward from corpus callosum in fimbriated pattern termed "Dawson fingers".
4. Another characteristic pattern is C shaped partial ring of enhancement created by rounded lesion interrupted by gyrus.
5. Lesions that have undergone some degree of cavitation are hypointense on T_1W termed "black holes".
6. Serial MRI can demonstrate progress of disease, e.g. increasing number of lesion.
7. MRI changes assume maximum diagnostic significance when they are consistent with the clinical findings.

Q. What are the **other demyelinating disorders**?

A. As follows:

- ADEM
- Leukodystrophies
- Tuberous sclerosis (patchy demyelination)
- Devic's disease (acute necrotising myelitis with optic neuritis)

- Schilder's disease (diffuse cerebral sclerosis. There may be cortical blindness, if occipital cortex is involved, cerebral deafness, quadriplegia, hemiplegia, dementia, pseudobulbar palsy.
- Tuberous sclerosis (patchy demyelination).

Q. What are the **causes** of bilateral upper motor neuron lesion involving the lower limbs?

A. As follows:

- Spinal cord compression
- MS
- MND (amyotrophic lateral sclerosis)
- Hereditary spastic paraplegia
- Transverse myeliltis
- Subacute combined degeneration
- Friedrich's ataxia
- Bilateral cerebral infarction
- Cervical myelopathy.

CEREBROVASCULAR DISEASE (CVD OR CVA)

CHIEF COMPLAINTS

- Weakness of right side of the body for … days
- Difficulty in speech and swallowing for … days
- Urinary incontinence for … days.

HISTORY

History of present illness: According to the statement of the attendant, the patient was reasonably well … days back. Suddenly in the early morning, while going to the toilet, he felt weakness of the right side of the body, initially in the upper limb, then the right lower limb, followed by fall to the ground. Since then, he is unable to move his right side of the body and cannot walk. The patient is also unable to speak and has difficulty in swallowing, which is more marked for liquid food. There is also urinary incontinence for the same duration but no bowel abnormality. There is no history of fever, loss of consciousness, convulsion, trauma to the head, nausea, vomiting and double vision.

History of past illness: He is hypertensive for 15 years and diabetic for 4 years. There is no history of any cardiac abnormality.

Family history: His father died of heart attack but his mother is alive in good health. His elder brother is also hypertensive.

Personal history: He is a smoker for the last 35 years, used to take 30 sticks/day.

Socioeconomic history: Mention accordingly.

Drug and treatment history: He used to take atenolol 50 mg/day and his diabetes is controlled by dietary modification.

GENERAL EXAMINATION

- The patient looks ill and anxious
- No anemia, jaundice, cyanosis, clubbing, koilonychia, leukonychia, edema
- No lymphadenopathy or thyromegaly
- Pulse: 85/min
- BP: 160/110 mm Hg
- Respiratory rate: 20/min
- Urinary catheter in situ.

SYSTEMIC EXAMINATION

Nervous System

1. **Higher cerebral functions:** The patient is conscious, but unable to speak fluently. Speech is slightly slurred.
2. **Cranial nerves:**

- 7th cranial nerve shows upper motor neuron lesion on the right side
- Rest of the cranial nerves are intact

3. **Motor system**:
   - Muscle tone is increased in the right upper and lower limbs
   - Muscle power: diminished in right upper and lower limbs, grade 4/5 in the lower limb and 3/5 in the upper limb.
   - Reflexes:

Jerks	Biceps	Triceps	Supinator	Knee	Ankle	Plantar
Right	Exaggerated	Exaggerated	Exaggerated	Exaggerated	Exaggerated	Extensor
Left	Normal	Normal	Normal	Normal	Normal	Flexor

   - There is patellar and ankle clonus on the right side
   - Coordination—impaired on the right lower limb
   - Gait—hemiplegic gait (during walking, the patient's right toes strike the ground and in an attempt to overcome this, the right leg is swung outwards at the hip, called circumduction).
4. **Involuntary movements:** Absent
5. **Sensory system:** Intact
6. **Fundoscopy:** Normal.

Cardiovascular System

- Pulse—85/min, regular
- BP—160/110 mm Hg
- JVP—normal
- Precordium—no abnormality

Examination of other systems—no abnormality detected.

SALIENT FEATURES

Mr. …, 62 years old, businessman, hypertensive, diabetic, smoker, hailing from …, presented with sudden weakness of the right side of the body … days ago, initially involving the right upper limb, then the right lower limb, followed by fall to the ground. Since then, he is unable to move his right side of the body and cannot walk. The patient is also unable to speak and has difficulty in swallowing, which is more marked for liquid food. There is also urinary incontinence for the same duration but no bowel abnormality. There is no history of fever, loss of consciousness, convulsion, trauma to the head, nausea, vomiting and double vision.

He is hypertensive for 15 years and diabetic for 4 years. There is no history of any cardiac abnormality. He is a smoker for the last 35 years, used to take 30 sticks/day. His father died of heart attack but his mother is alive in good health. His elder brother is also hypertensive. There is no family history of similar illness. He used to take atenolol 50 mg/day and his diabetes is controlled by dietary modification.

On Examination

General examination (mention as above)

Systemic examination (mention as above).

My diagnosis is hypertension with diabetes mellitus with CVD with right sided hemiplegia.

Q. What type of CVD is this?

A. Most likely, this is cerebral infarction (ischemic stroke) due to cerebral thrombosis.

Q. Why is it cerebral thrombosis?

A. Because, onset is slow. There is no history of vomiting, unconsciousness or convulsion.

Q. Why not cerebral embolism?

A. In cerebral embolism, onset is sudden (seconds to minutes), called stormy onset.

Q. Why not cerebral hemorrhage?

A. In cerebral hemorrhage, onset is sudden (seconds to minutes) and usually associated with loss of consciousness, vomiting or convulsion.

Q. Why not subarachnoid hemorrhage?

A. In subarachnoid hemorrhage, the patient is usually young. There is history of sudden severe headache mostly in the occipital region followed by vomiting and loss of consciousness. Features of meningeal irritation, like neck rigidity and Kernig's sign, are usually present. Fundoscopy shows subhyaloid hemorrhage (boot shaped concave).

Q. What is the likely site of lesion in your case?

A. Left internal capsule due to involvement of lenticulostriate branch of middle cerebral artery.

Q. What you have examined in the heart?

A. Any arrhythmia like atrial fibrillation. Also any valvular lesion, e.g. MS.

Q. Have you examined the neck? Why?

A. Yes. I have seen carotid bruit (thrombus from carotid may be dislodged and cause cerebral thrombosis).

Q. What investigations do you suggest?

A. As follows:

1. CT scan of the head (first investigation to be done)
2. Complete blood count with ESR
3. Blood sugar
4. Blood urea and serum creatinine
5. Serum lipid profile
6. Serum electrolyte
7. Chest X-ray P/A view
8. ECG
9. Source of the event:
   - Doppler study of extracranial/intracranial vessels
   - Echocardiography—transthoracic or transesophageal
   - MRA or CTA of the cerebral vessels
   - DSA of the cerebral vessels (Gold standard to find out AVM or aneurysm).
10. Other tests according to suspicion of cause:
    - For collagen vascular disease—ANA, anti-dsDNA, anti-cardiolipin and anti-phospholipid antibody
    - pANCA, cANCA
    - Coagulation screening, serum antithrombin III, protein C and protein S level
    - Others—red cell mass (PRV), chromatographic test in serum and urinary level of homocysteine or methionine (homocystinuria), TPHA and VDRL (syphilis).

RELATED QUESTIONS AND ANSWERS

Q. What is **stroke?** What are the **types** of stroke?

A. Stroke may be defined as sudden development of focal neurological deficit due to nontraumatic vascular cause, lasting more than 24 hours. It is of following types:

- Transient ischemic attack (TIA)—sudden neurological dysfunction due to cerebral ischemia lasting less than 24 hours and the patient recovers completely within 24 hours
- Stroke in evolution—the symptoms worsen gradually or in a step wise pattern over hours or days and the neurological deficit persists for more than 24 hours
- Completed stroke—clinical signs of neurological deficit are persistent
- Reversible ischemic neurological deficit (RIND)—neurodeficit persists for more than 24 hours, but recovers totally within 3 weeks
- Partial non-progressive stroke (PNS)—neurodeficit persists for more than 3 weeks, but is either partial or ends up with minimal residual deficit.

Q. What are the diseases included in **CVA?**

A. As follows:

- Cerebral hemorrhage
- Cerebral thrombosis
- Cerebral embolism
- Subarachnoid hemorrhage
- Hypertensive encephalopathy
- Cerebellar hemorrhage
- Cerebellar infarction.

Q. How to **treat** CVD?

A. As follows:

1. General measures:
   - Oropharyngeal suction
   - IV channel
   - Nasogastric tube feeding
   - Maintenance of nutritional status
   - Regular change of posture (2 hourly)
   - Care of bowel
   - Care of bladder (catheterization)
   - Care of mouth (to prevent fungal infection)
   - Care of eyes (tear naturale or taping of the affected eye shut).
2. Control of risk factors or cause, if any. For example:
   - Control of hypertension
   - Control of diabetes mellitus
   - Control of hyperlipidemia
   - Other treatment according to the cause.
3. If cerebral edema: Dexamethasone or mannitol.
4. Specific treatment according to the type of stroke (after CT scan):
   - Cerebral infarction—antiplatelet drugs (e.g. aspirin, clopidogrel). Cerebral vasodilator like vinpocetine should be given. If atrial fibrillation, heparin followed by warfarin should be considered
   - Cerebral hemorrhage—for massive hemorrhage, neurosurgical intervention may be required. Other treatment is symptomatic and supportive
   - Subarachnoid hemorrhage—nimodipine can be given, neurosurgical intervention is essential.

5. To reduce morbidity and improve quality of life:
   - Physiotherapy
   - Speech therapy
   - Occupational therapy.

Treatment of hypertension in stroke:

1. If the patient is known hypertensive—continue the antihypertensive if the BP is normal or high.
2. If the patient is not known to be hypertensive and BP is mildly or moderately high, then observe the patient and monitor BP for 7 to 10 days. If after this period BP is still high, then antihypertensive agents should be considered.
3. If the patient is not known to be hypertensive, antihypertensive drug should be started if:
   - There is evidence of target organ damage—such as hypertensive retinopathy or evidence of enlargement of heart.
   - BP is severe—>220/110 mm Hg
   - Co-morbidity—myocardial infarction, cardiac failure.
4. In CVD, following antihypertensive may be given:
   - ACEI or ARB
   - Calcium channel blocker
   - Beta blocker
   - Diuretics.

Q. What is the **prognosis** of CVA?

A. Prognosis depends on the type of lesion, site, extent of involvement and associated primary risk factors.

- Mortality rate is higher in intracerebral hemorrhage than embolic stroke
- In cerebral infarction, immediate prognosis is better, long-term prognosis depends upon extent of damage
- In cerebral hemorrhage, immediate prognosis is worse. In hemorrhagic stroke, 25% die within first 2 years, 10% die within first month. However, prognosis is better in the long run, when the hematoma resolves
- One-third of patients return to independent mobility, one-third becomes disabled requiring institutionalized care.

Q. What are the **complications** of acute stroke?

A. As follows:

- Raised intracranial pressure
- Hydrocephalus
- Aspiration pneumonia
- Convulsion
- Pressure sores
- DVT
- Pulmonary embolism
- Electrolyte imbalance
- Painful shoulder
- Urinary infection
- Constipation
- Depression and anxiety
- Alteration of sleep wake cycle.

Q. What are the causes of CVD in a **young patient?**

A. As follows:

- Mitral stenosis with atrial fibrillation (cerebral embolism from cardiac source)
- Other cardiac cause—PFO, VSD, TOF
- Antiphospholipid syndrome
- SLE
- Hematological disease—sickle cell anemia, polycythemia rubra vera, inherited deficiency of naturally occurring anti-coagulant (protein C, protein S, antithrombin III, factor V Leiden). In all these conditions, there is increased tendency of thrombosis.
- Vasculitis. Behcet's disease
- Vascular malformation—AVM, berry aneurysm causing SAH
- Arterial dissection
- In female—oral contraceptive pill, eclampsia
- Homocystinuria
- Syphilis
- Premature atherosclerosis may occur in familial hyperlipidemia
- Rarely, migraine may cause cerebral infarction
- Drugs like amphetamine, cocaine.

Q. What **investigations** should be done in a young patient with stroke?

A. See as above. For young patient, specific investigations are as follows:

- Chest X-ray, ECG and echocardiography (to exclude cardiac problem like MS with AF, other cardiac problem like PFO, TOF)
- CBC, ESR—(it will also exclude polycythemia rubra vera)
- Serum lipid profile—(in juvenile hyperlipidemia)
- For collagen vascular disease—ANA, anti-ds DNA, anti-cardiolipin and anti-phospholipid antibody
- Coagulation screening, serum antithrombin III, protein C and protein S level
- Others—red cell mass (PRV), chromatographic test in serum and urinary level of homocysteine or methionine (homocystinuria), TPHA and VDRL (syphilis).

Q. What are the **risk factors** for stroke?

A. Risk factors are variable for ischemic stroke and hemorrhagic stroke:

Risk factors for ischemic stroke:

1. Non-modifiable:
   - Age
   - Gender
   - Ethnicity or race
   - Genetics
   - Family history.
2. Modifiable:
   - Hypertension
   - Smoking
   - Lifestyle
   - Diabetes mellitus
   - Obesity
   - Heart disease (atrial fibrillation, ischemic heart disease, cardiomyopathy, etc.)
   - Dyslipidemia
   - Oral contraceptive pill

- Alcohol
- Previous history of stroke or TIA
- Carotid vessel atherosclerosis
- Atheromatous aortic arch
- Diseases like homocystinuria, hyperfibrinogenemia, deficiency of protein C, S and antithrombin III, polycythemia rubra vera, antiphospholipid syndrome, thrombotic thrombocytopenic purpura, sickle cell anemia, protein V Leiden syndrome, vasculitis (like poly arteritis nodosa, Wegener's granulomatosis, Takayasu's arteritis), migraine
- Abuse of cocaine, use of COX 2 inhibitor (slightly increased incidence of stroke).

Risk factors for hemorrhagic stroke:

- Hypertension
- AVM
- Aneurysm
- Amyloid angiopathy
- Cavernous angioma
- Anticogulant therapy
- Hypercoagulable disorder
- Drugs—cocaine, amphetamine
- Vasculitis—SLE, PAN, isolated CNS vasculitis
- Septicemia
- Moya-moya disease
- Hemorrhage into brain tumor.

Q. What are the causes of **recurrent hemiplegia**?

A. As follows –

1. CVD:
   - Atrial fibrillation
   - Hyperviscosity syndrome
   - Homocystinuria
   - Amyloidosis
   - Deficiency of protein C, S or antithrombin III
   - Polycythemia rubra vera
   - Antiphospholipid syndrome
   - Poly arteritis nodosa
   - Wegener's granulomatosis
   - Takayasu's arteritis.
2. Other causes:
   - Multiple sclerosis
   - Hemiplegic migraine
   - Epilepsy (Todd's palsy)
   - Hysteric hemiplegia.

Q. How to **prevent** stroke?

A. As follows:

- Risk factors like hypertension, diabetes mellitus, obesity, etc. should be identified and controlled
- Smoking and alcohol should be stopped
- Antiplatelet drug, e.g. aspirin
- Lifestyle modification—regular physical exercise, dietary modification

- Statin should be given to all patients
- If there is atrial fibrillation—treatment of primary cause and anticoagulation
- Treatment of primary cause.

Q. What is the **role of oral contraceptive pill** in stroke?

A. Low dose estrogen containing oral contraceptive pills do not increase the risk of stroke in healthy women, but can cause stroke if associated with other risk factors.

A BRIEF DISCUSSION ON DIFFERENT TYPES OF CVD

A. Cerebral thrombosis:

- The most common cause of CVA in middle aged or elderly (85%)
- The most common site is internal capsule and commonest vessel involvement is middle cerebral artery
- Risk factor—atherosclerosis, systemic hypertension, diabetes mellitus, polycythemia rubra vera, collagen vascular disease, dyslipidemia, smoking, obesity, oral contraceptive pill, alcohol, obesity, carotid artery occlusion
- Onset is insidious with stepwise progression. Commonly occurs during sleep or soon after waking
- Loss of consciousness is rare, but there may be headache, convulsion
- Neurological deficit depends on the site of lesion (see below)
- Shifting hemiplegia is absent (no migration of hemiplegic site)
- Carotid bruit with diminished pulsation may be present.

B. Cerebral embolism:

- Onset—very acute or stormy (develops quickly in seconds), during exertion or activity, no warning sign of TIA
- Site—left sided vascular lesion is common as left common carotid artery arises directly from the aorta. Left middle cerebral artery is commonly involved
- There is usually a source of embolus or vulvular heart disease with atrial fibrillation
- Neurological features may be increased due to associated vasospasm. Sometimes, features may be diminished or disappear due to dislodgement of the embolus. Shifting hemiplegia may occur
- Recovery—may be rapid
- Cause—atherosclerosis, mitral stenosis with atrial fibrillation, infective endocarditis, paradoxical embolism, myocardial infarction.

C. Cerebral hemorrhage:

- Usually occurs in elderly, cause of CVD is 15%
- Site—near internal capsule in basal ganglia. Other site—pons, thalamus, cerebellum and cerebral white matter
- Common vessel involved is the lenticulostriate branch of the middle cerebral artery
- Onset—usually sudden. There may be mental stress or strain
- Causes—almost all are hypertensive. Ruptured intracerebral aneurysm, blood dyscrasia, vascular anomaly like arteriovenous malformation, hemorrhage in a cerebral neoplasm
- The patient usually presents with severe headache, vomiting, convulsion, followed by unconsciousness
- On examination—conjugate deviation of eyes, Cheyne-Stokes breathing, features of raised

intracranial pressure, urinary retention. If pontine hemorrhage—pin point pupil, pyrexia and paralysis (3P). Other features depend on the site of hemorrhage
- Early recovery is unusual.

D. Subarachnoid hemorrhage:

- Common in young adults (apoplexy of the young), 5 to 10% stroke are due to subarachnoid hemorrhage. Sometimes in elderly, it is due to rupture of atherosclerotic aneurysm
- Cause—rupture of congenital berry aneurysm (commonest cause, in 80% cases). Common site—posterior communicating artery, anterior communicating artery or middle cerebral artery. Other causes are—head injury, leaking from arteriovenous malformation, rupture of cerebral angioma, rupture of mycotic aneurysm from infective endocarditis, blood dyscrasia, idiopathic in some cases. Any cause of cerebral hemorrhage can also cause
- Features—severe headache, usually in the occipital region, like struck by the hammer or thunderclap. There may be vomiting, convulsion, rapid loss of consciousness
- Neck rigidity and Kernig's sign are present. Fundoscopy shows subhyaloid hemorrhage with upward concavity (boot shaped)
- There may be paralysis of 3rd, 4th and 6th cranial nerves or monoplegia or hemiplegia due to pressure effect of berry aneurysm or vascular spasm
- Lumbar puncture and CSF study shows raised CSF pressure, which is frankly hemorrhagic. Xanthochromia is seen later on. CT scan is diagnostic. CT angiogram may be done
- Treatment—control of hypertension, nimodipine, surgical treatment.

E. Carotid hemiplegia:

- Occur in middle age or elderly
- Patients are often hypertensive and atherosclerotic
- History of TIA is commonly found
- There may be history of jaw claudication
- There may be kinking of the carotid artery, inequality of the pulse volume in two carotids or a bruit may be heard at the site of the block
- Ipsilateral visual disturbances (amaurosis fugax, means transient monocular blindness) and contralateral sensory motor deficit may be present.

Features of CVD according to site of involvement of different parts of brain:

1. Cortical:
   - Usually monoplegia
   - If lesion is extensive, contralateral hemiplegia may occur
   - Speech disturbance may be present, if lesion involves the dominant hemisphere
   - Jacksonian convulsions and headache may occur
   - There may be cortical type of sensory loss, e.g. astereognosis.
2. Subcortical:
   - Usually monoplegia
   - May be contralateral hemiplegia
   - Speech disturbance may be present
   - There may be loss of postural sensibility, tactile localization and discrimination of the affected limbs due to involvement of thalamocortical fibers.
3. Internal capsule:
   - Contralateral hemiplegia

- Hemianesthesia due to damage of the sensory fibers, homonymous hemianopia due to damage of visual fibers, both of which lie posterior to the pyramidal tract in internal capsule.
- Global aphasia in left sided lesion
- Seventh cranial nerve palsy on the side of palsy, UMN type.

4. Brainstem:
   - Symptoms are—vertigo, nausea, vomiting
   - Crossed hemiplegia, brainstem syndrome, pupilary abnormality, cerebellar involvement, gaze paralysis, Horner's syndrome
   - If pons is involved—there is deep coma, pin point pupil, hyperpyrexia, decerebrate or decortical rigidity, absence of lateral eye movement on head turning
   - If involvement of midbrain and medulla—there is loss of consciousness, quadriplegia, Cheyne-Stokes breathing, decerebrate rigidity.

BRAINSTEM SYNDROME

1. Weber syndrome: Ipsilateral paralysis of 3rd cranial nerve (LMN type) with contralateral hemiplegia (crossed hemiplegia). Paralysis of upward gaze is usually present. Lesion is at midbrain.
2. Millard-Gubler syndrome: Paralysis of 6th cranial nerve (LMN type) with or without 7th cranial nerve palsy (LMN type) with contralateral hemiplegia (crossed hemiplegia). Lesion is at pons.
3. Lateral medullary syndrome (posterior inferior cerebellar artery thrombosis, also called Wallenberg's syndrome): Patient presents with acute vertigo, nausea, vomiting and diplopia, cerebellar and other signs. Features depend on the precise structures damaged and may include:
   - **Ipsilateral:**
     i. Trigeminal lesion—diminished pain and temperature (due to the involvement of descending tract and nucleus of trigeminal nerve)
     ii. Cerebellar sign (due to the involvement of cerebellum and its connection)
     iii. Horner's syndrome (due to the involvement of descending sympathetic tract)
     iv. Palatal paralysis and diminished gag reflex (there may be hoarseness and dysphagia due to vocal cord paralysis due to IXth and Xth nerve lesion)
     v. Diplopia (VIth nerve involvement).
   - **Contralateral:**
     i. Loss of pain and temperature due to spinothalamic tract involvement (in the trunk, limbs, may be in face). It is called dissociated sensory loss.
   - When there is isolated occlusion of PICA, pyramidal pathways escape and there is no hemiplegia. However, in majority of the cases, there is vertebral artery involvement and pyramidal signs (hemiplegia) are present.
4. Medial medullary syndrome:
   - It is due to occlusion of lower basilar artery or verterbral artery or one of its medial branches. It is characterized by contralateral hemiplegia which spares the face, contralateral loss of vibration and joint position sense, ipsilateral paralysis and wasting of tongue.

Note Remember the following points:

- Damage to brainstem reticular activating system leads to coma
- Upper brainstem infarction (ventral pons) leads to the locked-in syndrome
- Pseudobulbar palsy may occur after lower brainstem infarction (medullary infarction, bilateral cerebral infarction).

Differences between different types of CVD:

Points	Cerebral hemorrhage	Cerebral thrombosis	Cerebral embolism
1. Age	Elderly	Middle age	Young
2. Sex	Male	Both male and female	More in female
3. Onset	Sudden	Slowly	More sudden (stormy)
4. Precipitating factor	During excitement, exertion	During sleep	During exertion
5. Features: » Headache » Vomiting » Convulsion » Unconsciousness » Neck stiffness » Blood pressure » Pulse » Shifting hemiplegia » Cheyne-Stokes breathing » Heart » Conjugate deviation of eyes	Features: » Severe » Common » Absent » Common » May be present » High » Low » Never » Usually present » Evidence of LVH » Usually present	Features: » Less » Less » Common » Variable » Absent » May be high » Normal » Never » Usually absent » Usually normal » Rare	Features: » Absent » Less » Rare » Rare » Absent » Normal » Irregular due to AF » May be present » Usually absent » AF or MS » Rare
6. Investigations: » CSF » CT scan	Investigations: » Hemorrhagic » Hematoma	Investigations: » Clear » Infarction	Investigations: » Clear » Infarction
7. Prognosis	Poor prognosis	Good prognosis	Good prognosis, recurrence is common

Q. What are the **causes of coma** or unconsciousness?

A. As follows—(remember the mnemonic **AEIOU DAMH**)

- **A**poplexy—cerebral hemorrhage, subarachnoid hemorrhage, etc.
- **E**pilepsy
- **I**nfection (e.g. encephalitis, meningitis, cerebral malaria, severe septicemia).
- **O**pium poisoning
- **U**remia (renal failure)
- **D**iabetes mellitus (ketoacidosis, hypoglycemia, lactic acidosis, HONC)
- **A**lcohol
- **M**etabolic—metabolic acidosis
- **H**ypoglycemia, hypoxemia, hypertensive encephalopathy, hepatic coma, hypothyroidism (myxedema coma), hyponatremia, hypothermia, hyperpyrexia, head injury.

Q. What is **funny turn**? What are the **causes**?

A. Funny turn means disturbance of consciousness which may be even transient. Causes are:

- Epilepsy
- Syncope
- Simple faints
- Cough syncope
- Effort syncope
- Micturition syncope.

- Carotid sinus syncope
- Cardiac dysrhythmias
- Autonomic failure
- Basilar migraine
- Non-epileptic attacks (pseudoseizure)
- Hyperventilation
- Breath holding
- Panic attack
- Choking attack
- Apneic episode
- TIA
- Drop attack
- Tonic attack
- Hydrocephalic attack
- Hypoglycemia
- Hypocalcemia
- Severe vertigo
- Cataplexy, narcolepsy, sleep paralysis
- Night terror in children
- Paroxysmal dyskinesia
- Carcinoid syndrome, scombroid poisoning
- Pheochromocytoma
- Drug reaction (e.g. oculogyric crisis).

Q. What is **drop attack**?

A. It is characterized by sudden, unpredictable weakness of lower limbs with falling to the ground without any warning signs, dizziness or loss of consciousness. It is common in middle aged women. It is due to sudden change in lower limb tone, presumably of brainstem origin, rather than thromboembolism.

Q. What is **coma vigil**?

A. It is a state of impaired consciousness with muttering. The unconsciousness is not such as to amount coma. It is observed in infectious fever such as typhoid, dengue or pneumonia.

FRIEDREICH'S ATAXIA

CHIEF COMPLAINTS

- Weakness of the lower limbs and difficulty in walking for … years
- Wasting of the muscles of the leg and foot for … years
- Tingling, numbness of the foot for … years

HISTORY

History of present illness: According to the statement of the patient, he was reasonably well … years back. Since then, he has been suffering from weakness of both lower limbs. His weakness is progressively increasing, which has become more severe and he is unable to walk without the help of others. He also experiences progressive wasting of the muscles of lower limbs, initially in the foot followed by the leg. The patient also complains of tingling and numbness in both lower limbs. There is no history of head or spine trauma, fever, headache, convulsion, loss of consciousness or incontinence of urine. His bowel and bladder habits are normal.

History of past illness: He suffered from repeated attacks of respiratory infection and occasional fever over the past few years.

Family history: There is no history of similar illness in the family members.

Socioeconomic history: Mention according to the statement of the patient.

Drug and treatment history: For these symptoms, he took some vitamins.

Personal history: He is a nonsmoker and nonalcoholic.

GENERAL EXAMINATION

- The patient is short, ill-looking and anxious
- There is pes cavus with cocking of toes, kyphoscoliosis and high arched palate
- Mildly anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema
- No thyromegaly or lymphadenopathy
- Pulse: 88/min
- BP: 110/80 mm Hg
- Respiratory rate: 24/min
- Temperature: 97ºF.

SYSTEM EXAMINATION

Nervous System

1. **Higher cerebral functions:**
   - Speech—scanning (or staccato speech)
   - No other abnormality.
2. **Cranial nerves**: Optic atrophy, reduced hearing. Other cranial nerves are normal.
3. **Motor system:**
   - There is wasting of muscles of both legs
   - Muscle tone—diminished in both the lower limbs

- Muscle power—normal in upper limb and diminished in the lower limbs
- Reflexes:

Jerks	Biceps	Triceps	Supinator	Knee	Ankle	Plantar
Right	Normal	Normal	Normal	Absent	Absent	Extensor
Left	Normal	Normal	Normal	Absent	Absent	Extensor

- Coordination—could not be done due to muscle weakness
- Rombergism—positive
- Gait—ataxic gait (cerebellar)
- Involuntary movement—absent.

4. **Sensory system:** vibration, position sense and two point discrimination are impaired in both the lower limbs. Other modalities of sensation are normal.
5. **Cerebellar signs:**
   - Speech—scanning
   - Horizontal nystagmus in both eyes, more in right side than left
   - Finger nose test—dysmetria, past-pointing
   - Co-ordination—could not be done due to muscle weakness
   - Gait—ataxic gait (cerebellar)
   - Dysdiadochokinesia—absent (or present)
   - Action tremor—absent (both action and intention tremor may be present)
   - Titubation—absent.

Cardiovascular System

- Pulse—88/min, regular
- BP—110/80 mm Hg
- Precordium—no abnormalities detected.

Examination of other systems reveals no other abnormalities.

SALIENT FEATURES

Mr …, 20 years old, student, normotensive, nondiabetic, nonsmoker, nonalcoholic, hailing from …, presented with weakness of both lower limbs for … years. His weakness is progressively increasing, which has become more severe and he is unable to walk without the help of others. He also experiences progressive wasting of the muscles of lower limbs, initially in the foot followed by the leg. The patient also complains of tingling and numbness in both lower limbs. There is no history of head or spine trauma, fever, headache, convulsion, loss of consciousness or incontinence of urine. His bower and bladder habits are normal. He suffered from repeated attacks of respiratory infection and occasional fever over the past few years. There is no history of similar illness in the family members. For his illness, he took some vitamins.

On Examination
General examination (mention as above)
Systemic examination (mention as above).

My diagnosis is Friedreich's ataxia.

Q. What are your **differential diagnoses?**

A. As follows:

- Multiple sclerosis
- Tabes dorsalis
- Spinocerebellar degeneration.

Q. What **investigations** should be done in Freidreich's ataxia?

A. As follows:

- CBC, ESR
- Blood sugar (high in 10%)
- Chest X-ray (cardiomegaly)
- ECG (arrhythmia)
- MRI of brain and spinal cord (shows atrophy of cerebellum and spinal cord)
- NCS (shows conduction velocity in motor fibers is normal or mildly reduced, but sensory action potentials are small or absent).

RELATED QUESTIONS AND ANSWERS

Q. What is **Friedreich's ataxia**? What are the **features**?

A. It is the most common type of hereditary ataxia, inherited as autosomal recessive trait, and in some cases inherited as autosomal dominant.

Features of Friedreich's ataxia are:

- Cause—unknown. Mutation of FRDA gene in chromosome 9. The mutation is abnormal expansion of trinucleotide repeat within a gene that code for protein 'Frataxin', whose function is to prevent intramitochodrial iron overloading
- Family history—may be present
- Usual onset—young, < 15 years (8 to 16 years)
- Presentations—progressive difficulty in walking (truncal ataxia and ataxia of lower limbs), weakness of lower limbs and dysarthria
- Signs are:
  - Cerebellar signs (dysarthria, nystagmus, intention tremor, ataxic gait, etc.)
  - Posterior column—absent vibration and position sense, positive Rhombergism
  - Corticospinal tract sign—plantar extensor, weakness
  - Peripheral nerve—absent reflexes in lower limb, wasting of muscles.
- Diabetes mellitus (common)
- Associated with kyphoscoliosis, pes cavus, cocking of toes, optic atrophy, spina bifida and hypertrophic cardiomyopathy (may cause sudden death), hearing loss
- Normal mentation (may have mild dementia)
- Prognosis—usually progresses slowly, death occurs before 40 years of age (usually 20 years after the onset of symptoms due to cardiac and respiratory complications)
- Become chair—bound 9 to 15 years after onset of symptoms. May be static and survive up to 60 years.

Q. What are the **sites** of lesion in Friedreich's ataxia?

A. As follows (there is progressive degeneration):

- Cerebellar lesion
- Spinocerebellar tract
- Posterior column lesion (loss of vibration and position sense) and dorsal root ganglia lesion
- Degeneration of peripheral sensory fibers
- Corticospinal tract lesion (lateral column lesion)
- Eye (primary optic atrophy).

Q. Why **absent tendon reflex**, but **extensor** plantar response?

A. Because of combination of pyramidal lesion, dorsal column and dorsal root lesion. Also, there is involvement of the peripheral sensory fibers that leads to sensory disturbance in the limbs and depressed tendon reflex.

Q. What are the causes of **pes cavus?**

A. As follows:

- Congenital
- Friedreich's ataxia
- Charcot-Marie-Tooth disease
- Hereditary motor and sensory neuropathy
- Spinocerebellar degeneration
- Peripheral neuropathy in childhood
- Old poliomyelitis (usually unilateral).

Q. What are the causes of **combined** cerebellar, pyramidal and dorsal column signs?

A. As follows:

- Multiple sclerosis
- Friedreich's ataxia
- Spinocerebellar degeneration
- Syphilitic meningomyelitis
- Arnold-Chiari malformation.

Note Remember the following points:

In young patient with pes cavus **plus** combination of cerebellar lesion (bilateral), UMN lesion (extensor plantar) and posterior column lesion (loss of vibration and position senses), is highly suggestive of Friedreich's ataxia.

Q. What are the different **types** of hereditary ataxias?

A. It may be of different types, with different patterns of inheritance:

1. Autosomal recessive:
   - Friedreich's ataxia
   - Ataxia telangiectasia
   - Ataxia with vitamin E deficiency.
2. Autosomal dominant:
   - Spinocerebellar ataxia type 1-28
   - Episodic ataxia
   - DRPLA (Dentatorubropallidoluysian atrophy).
3. X-linked:
   - FXTAS (Fragile X-associated tremor/ataxia syndrome).
4. Mitochondrial:
   - MELAS (Mitochondrial encephalomyopathy, lactic acidosis and stroke)
   - MERRF (Myoclonic epilepsy with ragged red tibers)
   - KSS (Kearns-Sayre syndrome).

PERIPHERAL NEUROPATHY

CHIEF COMPLAINTS

- Progressive weakness of the lower limbs for … months
- Heaviness and wasting of the lower limbs for the … months
- Pins and needles in the hands and feet for the … months.

HISTORY

History of present illness: According to the statement of the patient, he was reasonably well … months back. Since then, he has been suffering from progressive weakness of the lower limbs. Initially, the weakness was present in both feet. Then gradually it involved the legs and thighs. The severity has increased over the last few weeks. The patient now finds it difficult to walk and also feels a sense of heaviness in the lower limbs. He also noticed wasting of the muscles of the lower limbs. For the last … months, he also experiences pins and needles like sensation in the hands and feet. It is more marked at night and is progressively becoming severe leading to marked sleep disturbance. He cannot even keep the bed sheet on his legs. There is no history of any infection, joint pain or skin rash. His bowel and bladder habits are normal. He is a known diabetic for last 15 years and is on oral drugs.

History of past illness: Mention according to the patient's statement.

Personal history: He is a smoker for the last 20 years, used to take 20 cigarettes daily but not alcoholic.

Socioeconomic history: He is a government service holder and comes from a middle class family.

Drug and treatment history: He takes tablet Glipizide 5 mg twice daily for diabetes mellitus and multivitamin.

GENERAL EXAMINATION

- The patient is obese and anxious
- Mildly anemic
- No jaundice, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- Pulse: 88/min
- BP: 150/85 mm Hg in lying position, 140/80 mm Hg in standing position
- Temperature: Normal
- Respiratory rate: Normal.

SYSTEMIC EXAMINATION

Nervous System

1. **Higher cerebral functions:** Normal.
2. **Cranial nerves:** Intact, Fundoscopy—may be retinopathy.
3. **Motor system:**

- Muscle tone: Diminished in both the lower limbs, normal in upper limbs
- Muscle power: Diminished, grade 3/5 in the lower limbs, normal in upper limbs
- There is wasting of all the groups of muscle in the feet, legs and thighs
- Reflexes:

Jerks	Biceps	Triceps	Supinator	Knee	Ankle	Plantar
Right	Normal	Normal	Normal	Diminished	Absent	Equivocal
Left	Normal	Normal	Normal	Diminished	Absent	Equivocal

- Coordination: Impaired in the lower limbs
- Rombergism: Positive
- Gait: High stepping gait
- Involuntary movements: Absent.

4. **Sensory system:**
   - Both superficial and deep sensation—impaired upto mid thigh
   - Vibration and position sense—absent in both the lower limbs.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 52 years old, Government service holder, diabetic for 15 years, normotensive, smoker, nonalcoholic, hailing from …, presented with progressive weakness of the lower limbs for … months. Initially, the weakness was present in both feet. Then gradually it involved the legs and thighs. The severity has increased over the last few weeks. The patient now finds it difficult to walk and also feels a sense of heaviness in the lower limbs. He also noticed wasting of the muscles of the lower limbs. For the last … months, he also experiences pins and needles-like sensation in the hands and feet. It is more marked at night and is progressively becoming severe leading to marked sleep disturbance. He cannot even keep the bedsheet on his legs. There is no history of any infection, joint pain or skin rash. His bowel and bladder habits are normal. He is not vegetarian. He smokes about 20 cigarettes a day for the last 20 years. He gives no history of intake of drugs that may cause these symptoms. He takes Tab. Glipizide 5 mg twice daily for diabetes mellitus and multivitamin. There is no family history of such illness.

On Examination

General examination (mention as above)
Systemic examination (mention as above).

My diagnosis is diabetes mellitus with peripheral neuropathy.

Q. Could it be **MND**?

A. No. In MND, there is no sensory loss.

Q. What **investigations** should be done in polyneuropathy?

A. As follows:

- CBC, PBF (if macrocytosis is present, it indicates subacute combined degeneration due to vitamin B_{12} deficiency)
- Blood sugar
- Chest X-ray (to exclude bronchial carcinoma)
- Serum B_{12} and folate assay

- Renal (serum urea and creatinine) and hepatic function tests—if needed
- Bone marrow (if suspicion of B_{12} deficiency)
- Other investigations according to suspicion of causes (ANA and RA test)
- Nerve conduction studies (axonal or demyelinating).

RELATED QUESTIONS AND ANSWERS

Q. What are the **causes** of peripheral neuropathy?

A. As follows (mention the causes according to the age of the patient):

- Diabetes mellitus
- Nutritional deficiency (B_1, B_6, B_{12}, folic acid, pantothenic acid and vitamin E).
- Paraneoplastic sensory neuropathy (in bronchial carcinoma, lymphoma and multiple myeloma)
- Drugs (isoniazid, vincristine, phenytoin, amiodarone, statin, cisplatin, dapsone, nitrofurantoin)
- Alcoholism
- Guillain-Barré syndrome
- Infections (leprosy, HIV, typhoid and diphtheria)
- Collagen disease (SLE, polyarteritis nodosa and rheumatoid arthritis)
- Others—chronic renal failure (CRF), chronic inflammatory demyelinating polyneuropathy (CIDP)
- Idiopathic (in many cases).

Note Common causes of neuropathy:

- Diabetes mellitus
- Leprosy
- Alcohol
- Guillain-Barré syndrome
- Chronic renal failure
- Drugs like INH, vincristine
- Deficiency—vitamin B_{12}, B_1, nicotinic acid, B_6.

Q. Which part is **first involved** in peripheral neuropathy? Why?

A. Usually distal part of the limbs is commonly involved, because longer the nerve fiber earlier is the involvement. Since the nerve fibers supplying the distal parts of the limbs are longer, they are first affected.

Q. What are the causes of **painful neuropathy?**

A. As follows:

- Diabetes mellitus
- Nutritional (deficiency of vitamins B_1 and B_{12})
- Alcohol
- GBS
- Vasculitis
- Connective tissue disease
- HIV
- Uremic neuropathy
- Paraneoplastic sensory neuropathy
- Porphyria
- Arsenic or thallium poisoning.

Treatment: Tricyclic antidepressant, phenytoin, carbamazepine and topical capsaicin.

Q. What are the causes of **predominantly sensory neuropathy?**

A. As follows:

- Diabetes mellitus
- Leprosy
- Deficiency of vitamins B_1, B_6 and B_{12}
- Chronic renal failure
- Paraneoplastic neuropathy (in bronchial carcinoma)
- Drugs (INH, vincristine)
- Hereditary sensory neuropathy
- HIV
- Multiple myeloma.

Q. What are the causes of **predominantly motor neuropathy?**

A. As follows:

- Guillain-Barré syndrome, CIDP
- Charcot-Marie-Tooth disease
- Acute intermittent porphyria
- Chronic lead poisoning
- Diabetic amyotrophy
- Diphtheria
- Paraneoplastic syndrome
- POEMS (**P**eripheral neuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**-protein, **S**kin changes).

Q. What are the **mechanisms** of neuropathy?

A. As follows:

- Demyelination
- Axonal degeneration
- Wallerian degeneration (after section of nerve, axonal and myelin sheath degeneration)
- Compression (called entrapment neuropathy) and there is segmental degeneration at the site of compression
- Infarction of nerve—microinfarction of nerve due to arteritis of vessels supplying the nerve (found in diabetes mellitus and polyarteritis nodosa)
- Infiltration in nerve (found in leprosy, sarcoidosis and malignancy).

Q. What are the causes of **demyelination** and **axonal degeneration?**

A. As follows:

1. Causes of demyelination:
   - Guillain-Barré syndrome
   - Hereditary sensory motor neuropathy
   - Diphtheria
   - Diabetes mellitus.

2. Causes of axonal degeneration:
   - Toxic neuropathy (alcohol and drugs)
   - Diabetes mellitus
   - Paraneoplastic syndrome
   - IgG paraproteinemia
   - Hereditary
   - Vitamin deficiency.

Q. How to **differentiate** between demyelination and axonal degeneration?

A. By NCS and electromyography (EMG):

- In demyelination, there is slowing of nerve conduction, amplitude of nerve action potential (CMAP) is normal
- In axonal degeneration, the conduction velocity is normal as axonal continuity is maintained in surviving fibers, amplitude of CMAP is reduced. Using needle EMG, denervation on the affected muscles may be demonstrated.

Q. What is **mononeuritis multiplex** and what are the **causes** of it?

A. Involvement of multiple peripheral nerve or cranial nerve by a single disease is called mononeuritis multiplex. It is due to involvement of vasa nervorum or malignant infiltration of nerves. Causes are:

- Diabetes mellitus
- Leprosy
- Rheumatoid arthritis
- Vasculitis (SLE, polyarteritis nodosa)
- Amyloidosis
- Malignancy (carcinomatous neuropathy)
- Sarcoidosis
- HIV infection
- Wegener's granulomatosis
- Acromegaly
- Paraproteinemia
- Lyme disease
- Idiopathic multifocal motor neuropathy.

Q. What are the causes of **acute mononeuritis multiplex?**

A. As follows (usually vascular):

- Polyarteritis nodosa
- Diabetes mellitus
- Collagen disease (SLE, RA).

Q. What are the **types of neuropathy in DM?**

A. As follows:

- Commonly sensory neuropathy
- Mixed motor and sensory neuropathy
- Asymmetrical motor neuropathy (diabetic amyotrophy)
- Autonomic neuropathy
- Mononeuropathy
- Mononeuritis multiplex.

It may be symmetrical or asymetrical:

1. **Symmetrical**:
   - Distal symmetrical primary sensory polyneuropathy
   - Subacute or chronic proximal symmetrical motor neuropathy
   - Autonomic neuropathy.
2. **Asymmetrical**:
   - Diabetic amyotrophy
   - Cranial mononeuropathy or mononeuritis multiplex
   - Mononeuropathy involving trunks or limbs
   - Entrapment neuropathy.

Q. What is the **mechanism** of neuropathy in DM?

A. As follows:

- Axonal degeneration
- Patchy or segmental demyelination
- Involvement of intraneural capillaries.

Q. What is the **pathogenesis** of diabetic neuropathy?

A. As follows:

1. Metabolic theory: Increased neuronal concentration of glucose results in increased conversion of glucose to sorbitol. The resultant increase in diacylglycerol, protein kinase C and Na-K ATPase activity causes neuronal loss and demyelination.
2. Vascular theory: Increased aldose reductase activity causes decreased NO that results in reduced blood flow in vasa nervorum.
3. Altered metabolism of fatty acid.
4. Nutritional: Reduced concentration of nerve growth factor, vascular endothelial growth factor and erythropoetin.
5. Oxidative stress.

Q. What are the **causes of thickening of nerves?**

A. As follows:

- Leprosy
- Neurofibroma
- Amyloidosis
- Acromegaly
- Sarcoidosis
- Charcot-Marie-Tooth disease (hereditary motor and sensory neuropathy)
- Repeated friction or trauma
- Refsum disease
- Dejerine-Sottas disease (hypertrophic peripheral neuropathy).

Q. What are the causes of **autonomic neuropathy**?

A. As follows:

- Diabetes mellitus (commonest cause)
- Guillain-Barré syndrome
- Amyloidosis
- Toxin (vincristine)
- Paraneoplastic syndrome
- Porphyria
- AIDS
- Shy-Drager syndrome
- Riley-Day syndrome (familial dysautonomia)
- Hereditary sensory and autonomic neuropathy.

Q. How to **test autonomic function**?

A. As follows:

1. Simple reflex test (common in practice):
   - Heart rate responses to Valsalva maneuver (15 seconds) on R-R interval of ECG—ratio of longest to shortest R-R interval is normally 1.21 or more. If 1.20 or less, it is abnormal.
   - Heart rate responses to deep breathing (6 breaths over 1 minute)—maximum-minimum heart rate of 15 or more is normal, 11 to 14 is borderline and 10 or less is abnormal.

- Heart rate responses to standing after lying—ratio of R-R interval of 30th to 15th beats—if 1.04 or more it is normal, 1.01 to 1.03 is borderline and 1.00 or less is abnormal.
- Blood pressure response to standing—systolic BP fall (mm Hg) 10 or less is normal, 11 to 29 is borderline and 30 or more is abnormal.

2. Special tests:
   - Heart rate and blood pressure response to sustained hand grip
   - Heart rate variability using power spectral analysis of ECG monitoring
   - Heart rate and blood pressure variability using time (domain analysis of ambulatory monitoring)
   - MIBG (met-iodobenzylguanidine) scan of the heart.

Q. What is the **prognosis** of autonomic neuropathy in diabetes mellitus?

A. Development of autonomic neuropathy in diabetic mellitus is less clearly related with poor glycemic control than somatic neuropathy. Improved control of diabetes rarely improves the symptoms. Within 10 years of development of symptoms of autonomic neuropathy, 30 to 50% die from sudden cardiorespiratory arrest, cause of which is unknown. Patients with postural hypotension (a drop of systolic pressure > 30 mm Hg on standing from supine) have highest mortality.

GUILLAIN-BARRÉ SYNDROME

CHIEF COMPLAINTS

- Weakness of both lower limbs for … days
- Difficulty in walking for … days.

HISTORY

History of present illness: According to the statement of the patient, she was reasonably well … days back. Then she suffered from mild fever, cough and sore throat from which she recovered in 4 days. Adult 10 days later, she experiences weakness of both lower limbs. Initially at both feet, then sequentially involving the legs and the thighs. For … days, her weakness is gradually increasing and she feels difficulty in walking. For the last … days, she is completely bedridden and unable move her limbs, and experiences a sense of heaviness. Her bowel and bladder habits are normal. She does not have any breathing difficulty, nasal regurgitation or difficulty in swallowing. There is no history of trauma, operation, vaccination or previous episode of such illness.

History of past illness: Nothing significant.

Drug and treatment history: Nothing significant.

Personal history: She is married and has two sons. She is a nonsmoker.

Socioeconomic history: She comes from a lower middle class family.

Family history: Nothing significant.

GENERAL EXAMINATION

- The patient is bedridden, looks ill and anxious
- Mildly anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- Pulse: 88/min
- BP: 110/75 mm Hg
- Temperature: Normal
- Respiration: Normal.

SYSTEMIC EXAMINATION

Nervous System

1. **Higher cerebral functions**: Normal.
2. **Cranial nerves** including fundoscopy: Intact.
3. **Motor system:**
   - Muscle tone—diminished in both lower limbs
   - Muscle power is grade 1/5 in lower limbs and normal in the upper limbs
   - Wasting—Absent
   - Reflexes:

Jerks	Biceps	Triceps	Supinator	Knee	Ankle	Plantar
Right	Normal	Normal	Normal	Absent	Absent	Equivocal
Left	Normal	Normal	Normal	Absent	Absent	Equivocal

- Coordination—normal in upper limbs, could not be elicited in lower limbs
- Rombergism—could not be tested
- Gait—The patient is unable to walk.
- Involuntary movement—absent

4. **Sensory system**: No abnormality detected.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mrs …, 42 years old, housewife, normotensive, nondiabetic, nonsmoker, hailing from …, presented mild fever, cough and sore throat from which she recovered in 4 days. About 10 days later, she experiences weakness of both lower limbs. Initially at both feet, then sequentially involving the legs and the thighs. For … days, her weakness is gradually increasing and she feels difficulty in walking. For the last … days, she is completely bedridden and unable move her limbs, and experiences a sense of heaviness. Her bowel and bladder habits are normal. She does not have any breathing difficulty, nasal regurgitation or difficulty in swallowing. There is no history of trauma, operation, vaccination or previous episode of such illness. There is no family history of such illness. She was treated with vitamins by local doctors.

On examination
General examination (mention as above)
Systemic examination (mention as above).

My diagnosis is flaccid paraplegia, more likely due to Guillain-Barré Syndrome.

Q. What are the **causes** of flaccid paraplegia?

A. As follows:
- Guillain-Barré syndrome
- Motor neuropathy due to any cause
- Tabes dorsalis
- Freidreich's ataxia
- Progressive muscular atrophy (one type of MND)
- Acute inflammatory demyelinating polyradiculopathy (AIDP)
- HCR.

Q. What **investigations** do you suggest in GBS?

A. As follows:
- CSF analysis—typical finding is 'albuminocytological dissociation' (albumin may be very high, > 1000 mg %, lymphocytes are slightly raised or normal, < 20/mm^3. If lymphocyte is > 50, GBS is unlikely. CSF protein may be normal in first 10 days)
- Frequent monitoring of respiratory function tests (FVC, FEV_1, PEFR)
- Arterial blood gas analysis (as respiratory failure may occur at any time)
- Nerve conduction study (it shows slow conduction or conduction block. Demyelinating neuropathy, usually found after 1 week)

- Investigation to identify CMV, mycoplasma or campylobacter should be done
- Serum electrolyte.

Note

Triad of acute symmetrical ascending paralysis of limbs, areflexia and albumino: cytological dissociation in CSF is highly suggestive of GBS.

RELATED QUESTIONS AND ANSWERS

Q. What is **GBS**?

A. It is a postinfective demyelinating neuropathy of unknown cause, usually 1 to 3 weeks after respiratory infection, diarrhea and occasionally after vaccination or surgery. There is demyelination of peripheral nerve or spinal root, which is immunologically mediated. This may follow after infection with cytomegalovirus or mycoplasma or *Campylobacter jejuni*. GBS is monophasic and does not recur.

Q. What is the **cause** of GBS? What is the **mechanism**?

A. The GBS develops 1 to 3 weeks after respiratory infection or diarrhea (mainly by campylobacter) in 70% cases. Triggering factors may be *Campylobacter jejuni*, CMV, mycoplasma, herpes zoster, HIV, EBV infection.

There are 2 mechanisms:

1. Demyelinating (acute inflammatory demyelinating neuropathy, AIDP)
2. Axonal, which may be:
   - Motor (acute motor axonal neuropathy, AMAN)
   - Sensorimotor (acute motor and sensory axonal neuropathy, AMSAN).

There is predominantly cell-mediated inflammatory response to the myelin protein of spinal roots, peripheral and extra-axial cranial nerves. It is probably triggered by some infecting microorganisms. There is release of inflammatory cytokines that blocks nerve conduction and is followed by a complement mediated destruction of the myelin sheath and the associated axon.

It is a monophasic disease and does not recur.

Q. How does the patient of GBS usually **present?**

A. As follows:

- History of upper respiratory tract infection (URTI) or gastroenteritis (viral or bacterial)
- After 1 to 3 weeks, weakness of lower limbs that ascends over several weeks (ascending paralysis). It may advance quickly, affecting all the limbs at once and can lead to paralysis (quadriplegia)
- Respiratory paralysis in 20% case. Progressive respiratory involvement and paralysis is the main problem
- Paresthesia and pain in back and limbs may occur
- Facial and bulbar weakness
- Autonomic dysfunction—change of blood pressure, tachycardia, increased sweating, dysrhythmia may occur.

Q. What are the clinical **findings** in GBS?

A. As follows:

- Flaccid paralysis involving lower limbs and may involve all 4 limbs
- Loss of all reflexes
- Bilateral facial palsy (in 50% cases, unilateral in 25% cases)
- Sensory loss—minimum or absent
- Sphincter involvement (rare).

Note Remember the following points:

- Diffuse weakness with loss of all reflexes—a very striking finding in GBS
- GBS may be associated with Hodgkin's lymphoma
- Papilledema may develop
- May develop SIADH.

Diagnostic criteria for GBS:

Features required:

- Progressive weakness of both legs and arm
- Areflexia.

Features supportive:

- Progression over days, 4 weeks
- Relative symmetry
- Mild sensory symptoms or signs
- Cranial nerve involvement (bi-facial palsy)
- Recovery begins after 2 to 4 weeks
- Autonomic dysfunction
- Absence of fever
- Increased CSF protein with cell count <10/μL
- NCS—nerve conduction slowing or block.

Q. What are the variants of GBS?

1. **Regional:**
   - Fisher syndrome of ophthalmoplegia, ataxia and areflexia
   - Cervico-brachial-pharyngeal, often with ptosis
   - Oculopharyngeal weakness
   - Predominant paraparesis
   - Bilateral facial or abducens weakness with distal paresthesias
   - Ophthalmoplegia with GQ1b autoantibodies.
2. **Functional:**
   - Generalized ataxia without dysarthria or nystagmus
   - Pure sensory
   - Pure motor
   - Pandysautonomia
   - Axonal (AMAN).

Q. What are the **causes of motor neuropathy**?

A. As follows:

- Guillain-Barré syndrome
- Acute intermittent porphyria
- Diphtheria
- Diabetic amyotrophy
- Charcot-Marie-Tooth disease
- Chronic lead poisoning
- Paraneoplastic syndrome.

Q. How to **treat** GBS?

A. As follows:

- Ideally the patient should be treated in ICU and respiratory function should be monitored regularly (vital capacity and arterial blood gases). The patient may require artificial ventilation
- High dose intravenous gamma globulin should be given to all patients (it reduces the duration and severity). Dose is 400 mg/kg/day for 5 days. It is helpful, if given within 14 days. It may precipitate angina or myocardial infarction. In congenital IgA deficiency, it may cause allergic reaction
- Plasma exchange, if given within 14 days is equally effective in reducing the severity and duration of GBS
- Steroid has no proven value (may worsen). Methylprednisolone with immunoglobulin has no proven benefit
- Plasmapharesis may be required
- Physiotherapy is the mainstay of therapy
- Prevention of pressure sore and venous thrombosis
- Other symptomatic treatment.

Indication of ventilation:

- Impending respiratory failure—tachypnea, decrease in arterial O_2 tension < 85 mm Hg, FVC <20 mL/kg, maximum inspiratoy pressure <30 cm H_2O, maximum expiratory pressure <40 cm H_2O.
- FVC < 1.5 L
- PaO_2 < 10 κPa
- $PaCO_2$ > 6 κPa
- Rapid progression of disease
- Bulbar dysfunction
- Bilateral facial palsy
- Autonomic involvement.

Q. What are the **indications** of IV Ig in GBS?

- Incipient respiratory failure
- Patient unable to walk
- Oropharyngeal weakness
- Autonomic dysfunction
- Rapid progression of disease
- Ideally IV Ig should be given within 2 weeks of onset of disease.

Q. What are the **side effects** of IV Ig?

- Renal failure
- Proteinurea
- Nephrotic syndrome
- Aseptic meningitis
- Stroke
- Myocardial infarction
- CCF
- Anaphylaxis in IgA deficiency.

Q. What are the **adverse effects** of plasmapheresis?

A. As follows:

- The need for large bore venous axis
- Pneumothorax

- Infection
- Hemorrhage
- Hypotension
- Hypoprothrombinemia
- Cardiac arrhythmia
- Electrolyte imbalance.

Q. What are the **dangerous complications** of GBS **(cause of death)?**

A. As follows:

- Respiratory muscle paralysis. The patient may develop respiratory failure within hours
- Bulbar palsy (dysphagia, nasal regurgitation)
- Cardiac conduction block
- Cardiac arrythmia.

Q. What is the **prognosis** of GBS?

A. As follows:

- 80% recovery, may take several months (3 to 6 months). If axons have been damaged, the regeneration may require 6 to 18 months or longer
- 10% residual disability
- 3 to 5% die (in some study upto 10% death).

Adverse prognostic factors:

- Preceding GI infection
- > 60 years of age
- The most severe or rapidly evolving form of the disease (maximum disability within 7 days)
- Descending paralysis
- Bulbar weakness
- Autonomic dysfunction
- Asymmetrical weakness
- Very high CSF protein
- Evidence of widespread axonal damage
- Those requiring early and prolonged mechanical ventilatory assistance.

Good prognostic factors:

- Symmetrical involvement
- Slowly progressive
- Facial nerve involvement
- Young age
- Preceding hostory of respiratory infection
- Demyelinating disease
- No respiratory involvement
- Ascending paralysis
- Early treatment
- Early recovery.

Q. What is **Miller-Fisher syndrome?**

A. It is a variant of GBS characterized by triad of ophthalmoplegia, ataxia and areflexia. It is a rare disease. Antibodies to ganglioside GQ1b may be found.

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

CHIEF COMPLAINTS

- Numbness and paresthesia of both upper and lower limbs for … years
- Weakness and wasting of both lower and upper limb for … years.

HISTORY

History of present illness: According to the statement of the patient, he was reasonably well … years back. Since then, he noticed progressive numbness and paresthesia of both upper and lower limbs. It first started in the right lower limb and gradually involved the left lower limb and upper limbs in an ascending manner. He is also complaining of weakness and wasting of both upper and lower limbs which is of gradual onset. Initially it was progressively increasing, but for last … months, it is static. He does not give any history of headache, vomiting, neck pain. His bowel and bladder habits are normal.

History of past illness

Drug and treatment history

Personal history

Socioeconomic history

Family history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient is bedridden, looks ill and anxious
- Mildly anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- Pulse: 72/min
- BP: 110/70 mm Hg
- Temperature: Normal
- Respiration: Normal.

SYSTEMIC EXAMINATION

Nervous System

1. **Higher psychic functions:** Normal.
2. **Cranial nerves:** Intact.
3. **Motor system:**
   - Muscle tone—diminished in all four limbs
   - Muscle power—is grade 2/5 in all four limbs
   - Wasting—present
   - Reflexes:

Jerks	Biceps	Triceps	Supinator	Knee	Ankle	Plantar
Right	Absent	Absent	Absent	Absent	Absent	Equivocal
Left	Absent	Absent	Absent	Absent	Absent	Equivocal

- Coordination—could not be tested (because of muscular weakness)
- Rombergism—could not be tested (because of muscular weakness)
- Gait—the patient is unable to walk
- Involuntary movement—absent.

4. **Cerebellar functions:** Intact.
5. **Sensory system:**
   - Superficial and deep sensations are impaired
   - Vibration and position sense—absent.
6. **Fundoscopy:** Normal.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 48 years old, school teacher, normotensive, nondiabetic, nonsmoker, hailing from …, presented with numbness and paresthesia of both upper and lower limbs for … years. which first started in right lower limb and gradually ascending, then left lower limbs and upper limbs which is progressive in nature. He is also complaining of weakness and wasting of both upper and lower limbs which is of gradual onset. Initially it was progressively increasing, but for last … months it is static. He does not give any history of headache, vomiting, neck pain. His bowel and bladder habits are normal. There is no family history of such illness. He was treated with vitamins.

On examination
General examination (mention as above)
Systemic examination (mention as above).

My diagnosis is chronic inflammatory demyelinating polyneuropathy (CIDP).

Q. What are your **differential** diagnoses?

A. As follows:
- GBS
- Electrolyte imbalance (hypokalemia or hyperkalemia)
- Acute transverse myelitis.

RELATED QUESTIONS AND ANSWERS

Q. What is **CIDP**?

A. It is an autoimmune demyelinating disease of peripheral nerves characterized by weakness and sensory loss in limbs, peripheral nerve enlargement and high CSF protein. It affects young adults.

Q. What are the **presentations** of CIDP?

A. As follows:
- Common in young adult, males slightly more affected than female
- Onset is usually gradual, but sometimes subacute
- Features are like GBS
- Relapsing and remitting or progressive generalized neuropathy
- Sensory, motor or autonomic nerves can be involved, but the signs are predominantly motor. Some patients may present with pure sensory ataxia
- There may be external ophthalmoplegia in some cases
- A variant causes only motor involvement (multifocal motor neuropathy, MMN).

Q. What is the **difference** between CIDP and GBS?

A. CIDP is clinically similar to GBS except that it has a relapsing or steadily progressive course over months or years and that autonomic dysfunction is generally less common. It is less common than GBS. CIDP responds to steroid, while GBS does not.

Q. How to **diagnose**?

A. As follows:

- CSF examination (high protein, acellular)
- NCV of peripheral nerves—GBS like feature (marked slowing of motor and sensory conduction, and focal conduction block). Signs of partial denervation may be found due to secondary axonal degeneration
- MRI (plaques resembling multiple sclerosis are found in brain and spinal cord in some cases)
- Nerve biopsy (shows segmental demyelination).

DIAGNOSTIC CRITERIA OF CIDP

1. **Mandatory clinical criteria:**
   - Progressive or relapsing muscle weakness for 2 months or longer
   - Symmetrical proximal and distal weakness in upper or lower extremities
   - Hyporeflexia or areflexia.
2. **Mandatory laboratory criteria**:
   - Nerve conduction studies with features of demyelination motor nerve conduction <70% of lower limit of normal
   - Cereborspinal fluid protein level >45 mg/dL, cell count <10/μL.
   - Sural nerve biopsy with features of demyelination and re-myelination including myelinated fibre loss and perivascular inflammation.
3. **Mandatory exclusion criteria:**
   - Evidence of relevant systemic disease or toxic exposure
   - Family history of neuropathy
   - Nerve biopsy findings incompatible with diagnosis.

Q. How to **treat**?

A. Treatment of CIDP depends on severity of disease:

1. **Mild deficit—**follow-up only, there may be spontaneous recovery:
2. **Functionally significant deficit:**
   - Prednisolone 60 to 80 mg daily for 2 to 3 months or until response occurs. If no response in 3 months, then higher dose may be tried. After response, steroid is gradually tapered, but low dose steroid may be needed to continue for a long time.
   - Intravenous immunoglobulin (0.4 g/kg/day for 5 days)—usually used as an initial treatment with steroid
   - Plasma exchange—2 to 3 treatment per week for 6 weeks may be done
   - Others—if the above treatment fails, then immunosuppressive agents like azathioprine, methotrexate, cyclosporine or cyclophosphamide may be given
   - Multifocal motor neuropathy (MMN) is best treated by IV Ig.
3. **Severe disease, non-ambulatory:** Plasma exchange 2 to 3/week for 6 weeks and prednisone 60 to 80 mg/day.

Q. What is the **prognosis**?

A. Progress is variable. With drug therapy, most CIDP cases run a mild course over many years. There is occasional spontaneous recovery with time, but the disorder frequently follows progressive course leading to severe functional disability.

MYASTHENIA GRAVIS

CHIEF COMPLAINTS

- Weakness after activity for … months
- Difficulty in speaking, chewing and swallowing for … months
- Drooping of the upper eyelids after activity for … months.

HISTORY

History of present illness: According to the statement of the patient, she was reasonably well … months back. Since then, she noticed extreme weakness following activity or exercise. These symptoms are usually more marked towards the end of the day. She also noticed difficulty in chewing, swallowing, speaking and drooping of the upper eyelid following activity for … months. There is no history of any abnormality of sensation, fever, weight loss, tremor or involuntary movements, skin rash, joint pain or swelling. Her bowel and bladder habits are normal. She is normontensive and nondiabetic.

History of past illness: Mention according to the patient's statement.

Drug and treatment history: There is no history of taking any offending drug (e.g. D-penicillamine, etc.).

Personal history: Mention according to the patient's statement.

Socioeconomic history: Mention according to the patient's statement.

Family history: Mention according to the patient's statement.

GENERAL EXAMINATION

- Ill looking and anxious
- Bilateral partial ptosis: Present
- Mildly anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- Pulse: 76/min
- BP: 120/80 mm Hg
- Temperature: Normal
- Respiration: Normal.

SYSTEMIC EXAMINATION

Nervous System

1. **Higher cerebral functions:** Normal
2. **Cranial nerves including fundoscopy:** Normal
3. **Motor system:**
   - Muscle tone—normal
   - Muscle power—grade 4/5 in all four limbs.
   - Fatigability test (Ceiling test)—There is worsening of ptosis after sustaining upward gaze. Weakness of extraocular muscles of both sides (there may be double vision)

- Counting test—When the patient is asked to count 1 to 100, voice becoming low and ill distinct.
- Ice on eyes test
- Reflexes:

Jerks	Biceps	Triceps	Supinator	Knee	Ankle	Plantar
Right	Normal	Normal	Normal	Normal	Normal	Flexor
Left	Normal	Normal	Normal	Normal	Normal	Flexor

- Coordination—normal
- Rombergism—normal
- Gait—normal
- Involuntary movement—absent.

4. **Cerebellar function:** Intact
5. **Sensory system:** Intact.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mrs …, 40 years old, housewife, normotensive, nondiabetic, nonsmoker, hailing from …, presented with extreme weakness following activity or exercise for … months. These symptoms are usually more marked towards the end of the day. She also noticed difficulty in chewing, swallowing, speaking and drooping of the upper eyelid following activity for … months. There is no history of any abnormality of sensation, fever, weight loss, tremor or involuntary movements, skin rash, joint pain or swelling. Her bowel and bladder habits are normal. There is no history of taking D-penicillamine, ciprofloxacin, etc. There is no family history of such illness.

On examination
General examination (mention as above)
Systemic examination (mention as above).

My diagnosis is myasthenia gravis.

Q. What are your **differential diagnoses?**

A. As follows:
- Eaton Lambert syndrome
- Drug induced myasthenia
- Polymyositis
- Hypokalemic periodic paralysis.

Q. What **investigations** should be done in myasthenia gravis?

A. As follows:
- Complete blood count and ESR
- Chest X-ray (to exclude bronchial carcinoma)
- CXR right lateral view and CT scan of chest (to exclude thymoma)
- Edrophonium (Tensilon) test
- Vital capacity
- Serum acetylcholine receptor antibody (anti-AChR antibody, found in 80 to 90% patients with generalized myasthenia gravis. In pure ocular MG, this is present in 50%).

- Serum anti-MuSK antibody (antibody against muscle specific receptor tyrosine kinase, present with predominantly bulbar, facial and neck muscle involvement). It is positive in anti-AChR antibody negative patient and in pure ocular MG
- RNS—(progressive decremental response to repetitive nerve stimulation at 5 to 10 Hz)
- Single fiber EMG—evidence of neuromuscular blockade in the form of jitter and blocking of motor action potentials
- To see other associations—thyroid function test, antithyroid antibody, antiskeletal muscle antibody (suggest presence of thymoma), ANA, rheumatoid factor, serum CPK, antibody against intrinsic factor.

Q. What is **Tensilon test**?

A. 2 mg edrophonium is injected initially to see any untoward side effect. If no side effect, another 8 mg is given after half a minute. Improvement in muscle power occurs within 30 seconds and persists for up to 2 to 3 minutes. Sensitivity is 80%. Occasionally, there may be bronchospasm and syncope. Resuscitation facilities must be available. Atropine should be kept ready.

Q. What is the finding in **repeated nerve stimulation test (RNS)**?

A. It shows more than >10% decrement at 3 Hz.

RELATED QUESTIONS AND ANSWERS

Q. What is **myasthenia gravis?**

A. Myasthenia gravis is an autoimmune disease of skeletal muscle due to antibody against post-synaptic nicotinic acetylcholine receptor (AChR), characterized by fluctuating weakness specially ocular, facial, neck and bulbar muscles following activity. This antibody blocks neuromuscular transmission by depletion of post-synaptic receptors.

Below the age of 50 years, it is more common in women and associated with other autoimmune disease and thymic hyperplasia. Over 50 years, it is common in men and associated with thymic atrophy or thymic tumor.

Q. What is the **pathology** in MG?

A. Myasthenia gravis is caused by IgG antibodies against acetylcholine receptor protein. Immune complex of anti-AChR IgG and complement are deposited in the post-junctional membrane of the neuromuscular junction, which block neuromuscular transmission and initiate a complement mediated inflammatory response, which reduces the number of acetylcholine receptors and damages the end plate.

Thymic hyperplasia occurs in 70% myasthenic patient below the age of 40 years. In 10 to 15% cases, thymoma is present, incidence increases with age. Antibodies to striated muscles can be found in these patients.

Young patients without thymoma have an increased association with HLA-B8 and DR3.

Q. Which **muscles are commonly involved** in MG?

A. Muscle groups involved in order are—extraocular, bulbar (swallowing or chewing), face, neck, limb girdle and trunk. Cardiac muscle is not affected.

Q. Name one **drug** which can cause myasthenia gravis.

A. Penicillamine, (IFN-α also).

Q. What is **ice on eyes test?**

A. Ice cube is placed on patient's eyes and wait for 2 minutes or upto maximum tolerability. Ptosis is improved.

This test is highly specific and sensitivite in myasthenic diplopia.

Q. What are the **features** of myasthenia gravis? What **bedside tests** are done in MG?

A. Increasing muscular fatigue or weakness following activity. Following bedside test can be done:

- Ask the patient to count from 1 to 50—voice deteriorates and becomes nasal
- Ask to look straight or at the ceiling—ptosis will occur
- Ask the patient to close the eye tightly—after some time eyelids separate (peek) to show white sclera. This is called peek sign.

Note Remember the following:

Reflexes are normal.

Q. What is **myasthenic crisis**?

A. It is the exacerbation of symptoms of myasthenia gravis. May be severe and require artificial ventilation in 10% cases. The patient with bulbar and respiratory involvement are prone to respiratory infection. It may occur in patients who are getting no or inadequate treatment, due to low dose or following development of drug resistance. Precipitating factors are exertion, extremes of temperature, respiratory infection and surgery. The patient should be closely monitored for pulmonary function and should be treated in ICU. Treatment includes:

- Respiratory assistance and pulmonary physiotherapy
- Stop all cholinesterase inhibitors
- Plasmapheresis or IV immunoglobulin
- Antibiotic, if there is infection.

Q. What is **cholinergic crisis**?

A. Overdose of anticholinesterase drugs may cause cholinergic crisis, which is due to depolarization block of motor end plates. Features of cholinergic crisis are muscle fasciculation, paralysis, pallor, sweating, excessive salivation, lacrimation, bronchial secretion, small pupil (meiosis), abdominal colic, diarrhea, urinary incontinence, etc.

There may be respiratory insufficiency, confusion and collapse. Infection, diarrhea, aminoglycoside, penicillamine, steroid, etc may precipitate the crisis. Edrophonium should be avoided in these patients.

Q. How to **differentiate** between myasthenic crisis and cholinergic crisis?

A. The clinical features are as above. In both cases, patient complains of weakness.

- But muscarinic features are present only in cholinergic crisis, but absent in myasthenic crisis.
- Pupil in constricted or small in cholinergic crisis, but normal in myasthenic crisis.
- In myasthenic crisis—edrophonium causes quick improvement.

Q. How to **treat** MG?

A. As follows:

1. Symptomatic: Anticholinesterase drugs, e.g. pyridostigmine 60 mg tablet (4 to 16 tablets in divided doses up to five times a day). Duration of action is 3 to 4 hours. It prolongs the action of acetylcholine by inhibiting the action of acetylcholinesterase (side effects—overdose can cause cholinergic crisis characterized by severe muscle weakness. Muscarinic side effects like excessive salivation, lacrimation, bronchial secretion, abdominal pain, diarrhea, miosis, urinary incontinence, etc. Oral atropine 0.5 mg helps to reduce this.
2. Definitive:
   - Thymectomy—for all patients with thymoma and thymic hyperplasia.
   - Plasmapheresis—given in severe myasthenia or myasthenic crisis or preoperative preparation. A course of 5 exchanges, each of 3 to 4 liters fluid is given over a period of 2 weeks.

- Intravenous immunoglobulin: It is an alternative to plasma exchange in short-term treatment of severe myasthenia. Usual dose is 0.4 g/kg daily for 5 days. Improvement occurs in 70% cases. Side effects are headache and fluid overload, flu-like symptoms and anaphylaxis with IgA deficiency.
- Steroid: Initially there may be marked exacerbation of myasthenic symptoms and treatment should be initiated in hospital. To minimize the side effect, low dose prednisolone initially 5 mg/day, increase 5 mg/week up to 1 mg/kg. Continued for 1 to 3 months, then gradually modified to an alternate day regimen over the course of additional 1 to 3 months. On remission, reduce the dose (may take months). About 70% patients improve with steroid. Azathioprine may be added (2.5 mg/kg daily) or weekly methotrexate may be given. Sometimes, IV methylprednisolone may be tried.
- Other immunosuppressive agents, e.g. azathioprine (2.5 mg/kg daily), mycophenolate mofetil may be given.

Q. What are the **exacerbating factors** of MG?

A. Exercise, infection, emotion, change of climate, pregnancy, magnesium enema, drugs (aminoglycosides, penicillamine, propranolol, morphine, barbiturates, procanamide, quinidine, ciprofloxacin, quinine, antiarrhythmic drugs).

Q. What is the **role of thymectomy**?

A. Thymectomy should be performed in any antibody positive patient under 45 years with symptoms not confined to extraocular muscles, unless the disease has been established for more than 7 years. If thymoma is present, thymectomy is necessary to prevent tumor spread. If there is no thymoma, thymectomy is still beneficial in 60% patients and some patients go into drug free remission. However, the improvement is noticed 1 to 10 years after surgery.

Q. What is the **prognosis** after thymectomy?

A. Thymectomy improves prognosis, more so in women than men with positive AChR antibodies, even in patients without a thymoma.

Cases positive for anti-MuSK antibodies—do not improve following thymectomy. For these patients, plasmapheresis is the choice of treatment.

Q. What **drugs** should be avoided in MG?

A. Aminoglycoside, penicillamine, ciprofloxacin, quinine, antiarrhythmic drugs.

Q. What diseases are **associated** with MG?

A. Since MG is an autoimmune disease, it may be associated with other autoimmune diseases like thyrotoxicosis, hypothyroidism, diabetes mellitus, dermatomyositis, rheumatoid arthritis, SLE, Sjogren's disease, pernicious anemia, sarcoidosis, pemphigus, etc.

Q. What is **Eaton-Lambert syndrome (LEMS)**?

A. It is a paraneoplastic syndrome characterized by proximal muscle weakness, wasting and easy fatigability. It commonly involves the lower limbs, but may involve any muscle. Bulbar symptoms are rare (unlike MG).

Cause: There is defect in acetylcholine release at the neuromuscular junction, thought to be due to an autoantibody against P/Q type voltage gated calcium channel (VGCC—present in 90% case) on the motor nerve terminal. It is commonly due to small cell carcinoma of lung. May be associated with or may precede 1 to 2 years before the manifestations of carcinoma.

Features of LEMS:

- There are diminished or absent tendon reflexes (cardinal sign), appears immediately after sustained contraction of relevant muscle
- There is transient improvement in muscle strength and deep tendon reflexes following brief exercise. Muscle power increases after repeated activity (reverse of myasthenia gravis).

Investigation: EMG is diagnostic. There is progressive incremental response following repeated stimulation (reverse of myasthenia gravis, where there is progressive decremental response).

Treatment:

- Prednisolone plus azathioprine may be helpful
- Occasionally plasmapheresis
- 3, 4 diaminopyridine (DAP) is given
- Guanidine hydrochloride may help
- IV immunoglobulin
- No response to anticholinesterase drug. However anticholinesterase (pyridostigmine or neostigmine) either alone or in combination with guanidine hydrochloride shows variable response
- Treatment of primary cause (e.g. bronchial carcinoma).

Q. What are the **differences** between Eaton-Lambert syndrome and myasthenia gravis?

A. As follows:

Topic	Eaton-Lambert syndrome	Myasthenia gravis
1. Onset	From limbs	With ptosis
2. Course	Limbs to eyes	Eyes to limbs
3. Association	Malignancy, commonly small cell carcinoma of lung	Thymoma
4. Outcome of exercise	Improvement	Aggravate
5. RNS (EMG)	Incremental	Decremental
6. AChR antibody	Absent	Present

SPASTIC PARAPLEGIA (CORD COMPRESSION)

CHIEF COMPLAINTS

- Weakness of both lower limbs and difficulty in walking for … months
- Inability to void urine for … months
- Low back pain for … months
- Tingling and numbness of both lower limbs for … months.

HISTORY

History of present illness: According to the statement of the patient, he was reasonably well … months ago. Since then, he has been suffering from weakness of both lower limbs, which is gradually increasing and now he is unable to move his lower limbs and is unable to walk without the help of others. He also complains of difficulty in micturition and urinary incontinence for the last … days. The patient also complains of low back pain for … months, which is increased with even minor activities and on movement. For the last … months, he also experiences tingling and numbness on both lower limbs, more on right than left. There is no history of trauma, fever, weight loss, cough, burning in micturition or pain in other areas. His bowel habit is normal. Other systemic enquiry revealed no complaints.

History of past illness: He has no such events earlier, no visual compliants, and no history of vaccination.

Family history: There is no history of similar illness in his family.

Drug and treatment history

Personal history

Socioeconomic history: Mention according to the patient's statement.

GENERAL EXAMINATION

- Ill looking, anxious and bedridden
- Mildly anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- Urinary catheter in situ
- Pulse: 72/min
- BP: 120/70 mm Hg
- Temperature: Normal
- Respiration: Normal.

SYSTEMIC EXAMINATION

Nervous System

1. **Higher cerebral functions:** Normal
2. **Cranial nerves including fundoscopy:** Intact
3. **Motor system:**
   - Muscle tone—increased in both lower limbs, normal in both upper limbs

- Muscle power—diminished (grade 0/5) in both lower limbs, normal in both upper limbs.
- Wasting—absent
- Reflexes:

Jerks	Biceps	Triceps	Supinator	Knee	Ankle	Plantar
Right	Normal	Normal	Normal	Exaggerated	Exaggerated	Extensor
Left	Normal	Normal	Normal	Exaggerated	Exaggerated	Extensor

- Coordination—normal in upper limbs, heel-shin test could not be done due to weakness
- Rombergism—could not be evaluated
- Gait—could not be evaluated
- Involuntary movement—absent

4. **Cerebellar functions:** Intact
5. **Sensory system:** Sensory perception of all modalities is impaired below 10th thoracic dermatome and intact above it. There is some paresthesia along the T_{10} dermatome.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 40 years old, businessman, normotensive, nondiabetic, nonsmoker, hailing from …, has been suffering from weakness of both lower limbs, which is gradually increasing and now he is unable to move his lower limbs and is unable to walk without the help of others. He also complains of difficulty in micturition and urinary incontinence for the last … days. The patient also complains of low back pain for … months, which is increased with even minor activities and on movement. For the last … months, he also experiences tingling and numbness on both lower limbs, more on right than left. There is no history of trauma, fever, weight loss, cough, burning in micturition or pain in other areas. His bowel habit is normal. There is no history of such illness in his family.

On examination
General examination (mention as above)
Systemic examination (mention as above).

My diagnosis is spastic paraplegia, more likely due to cord compression.

Q. Why is it spinal cord compression?

A. Because, there are:
- UMN sign (spastic paraplegia) in both lower limbs
- Sensory loss below 10th thoracic segment
- Patient has radicular pain (low back pain)
- Pain and sensory symptom precedes weakness and urinary incontinence.

Q. What is the site of your lesion?

A. At the level of 10th thoracic spinal cord segment, 7th thoracic vertebra (to find the site, see below).

Q. What are your differential diagnoses?

A. As follows:
- Demyelinating disease (Multiple sclerosis, ADEM)
- Herniated intervertebral disc
- Tumor
- Subacute combined degeneration (SCD).

Q. Why not **MND?**

A. Because, in MND there will be:
- No sensory loss (very important sign)
- No pain
- No sphincteric disturbance
- Fasciculation is present
- Age (usually above 40 years).

Q. Could it be due to **SCD**?

A. Unlikely, as in SCD there will be:
- No pain
- No sphincteric disturbance
- Peripheral neuropathy
- Posterior column lesion (loss of vibration and position sense)
- Knee and ankle jerk absent (knee jerk may be brisk, plantar may be extensor)
- Romberg's sign is positive
- Others—anemia and smooth shiny tongue with atrophy of papilla, dementia.

Q. Could it be due to **Friedreich's ataxia?**

A. Unlikely, as in Friedreich's ataxia:
- Occurs in early age, before 25 years
- Pes cavus and kyphosis
- Loss of knee and ankle jerk, plantar is extensor
- Signs of cerebellar lesion
- Signs of posterior column lesion (loss of vibration and position sense)
- Other findings—optic atrophy, high arched palate, deafness and cardiomyopathy.

Q. What do you think the **causes of cord compression** in this case?

A. The causes may be:
- Tuberculosis of spine (Pott's disease)
- Lymphoma
- Abscess (paravertebral)
- Neoplastic lesions, such as meningioma, neurofibroma, glioma, metastasis.

Q. What **investigations** should be done in spastic paraplegia?

A. As follows:
- X-ray of lumbodorsal spine (anteroposterior and lateral view)
- MRI of dorsal spine
- Lumbar puncture and cerebrospinal fluid (CSF) study
- Other test according to cause (e.g. tuberculosis and myeloma)
- Myelogram (not done nowadays, as CT or MRI is most preferable).

RELATED QUESTIONS AND ANSWERS

Q. What are the **symptoms** of spinal cord compression?

A. As follows:
1. Pain—localized over the spine or in a root distribution, may be aggravated by coughing, sneezing or straining.
2. Sensory—paresthesia, numbness or cold sensations, especially in the lower limbs, which spread proximally often to a level on the trunk.

3. Motor—weakness, heaviness or stiffness of the limbs, most commonly the legs.
4. Sphincter—retention followed by urinary incontinence.

Q. What are the **cardinal signs** of spinal cord compression?

A. As follows:

- UMN sign (spastic paraplegia) below the level of compression and LMN sign at the level of compression
- Segmental sensory loss (sensory loss up to a particular segmental level).

Other features of spinal cord compression:

- Sphincter disturbance—common (urinary retention and loss of bladder control)
- Root pain—frequent at the site of compression
- Pain radiates in a band around the chest (thoracic compression).

Q. What are the causes of **spastic paraplegia**?

A. As follows (remember the age and also sensory loss):

- Spinal cord compression due to any cause (see below)
- Demyelinating disease (MS), ADEM
- MND (middle aged or elderly)—amyotrophic lateral sclerosis, primary lateral sclerosis
- Friedreich's ataxia (early age)
- Hereditary spastic paraplegia
- Subacute combined degeneration (SCD)
- Transverse myelitis
- Tropical spastic paraplegia
- HIV myelopathy
- Sarcoidosis
- SLE.

Q. What are the **most common causes** of spastic paraplegia?

A. As follows (**7 T**):

- **T**rauma
- **T**uberculosis (Pott's disease)
- **T**umor (meningioma, neurofibroma, lymphoma, leukemia, myeloma, glioma)
- **T**ransverse myelitis
- **T**abes dorsalis
- **T**welve (B_{12} deficiency)
- **T**hrombosis.

Q. What are the causes of **spinal cord compression** according to the site of lesion?

A. As follows:

1. Vertebral lesion (extradural, 80%):
   - Trauma
   - Intervertebral disc prolapse
   - Tuberculosis of spine (Pott's disease)
   - Lymphoma
   - Secondary deposit (elderly)
   - Multiple myeloma (elderly)
   - Abscess (paravertebral)
   - Extramedullary hemotopoiesis in β thalassemia major.

2. Meningeal lesion (intradural, extramedullary, 15%):
   - Meningioma
   - Neurofibroma
   - Ependymoma
   - Secondary deposit (elderly)
   - Lymphoma
   - Leukemia
   - Epidural abscess.
3. Spinal cord lesion (intradural, intramedullary, 5%):
   - Glioma
   - Ependymoma
   - Metastasis
   - Syringomyelia
   - Hematomyelia.

Q. What are the causes of spastic paraplegia due to **cerebral lesion**?

A. As follows:
- Parasagittal meningioma (usually falx meningioma)
- Thrombosis of superior longitudinal sinus
- Thrombosis of unpaired anterior cerebral artery
- Multiple cerebral infarction
- Hydrocephalus
- Trauma
- In children, cerebral palsy (cerebral diplegia).

Q. What are the **features** of cerebral lesion causing paraplegia?

A. As follows:
- There is bladder disturbance (urinary retention)
- Cortical type of sensory loss
- Other features—headache, vomiting, convulsion, Jacksonian fit.

Note Remember the following:

Lower limbs and micturition center are represented in the paracentral lobule. Hence lesion in this area produces paraplegia and bladder dysfunction

Q. What are the **non-compressive causes** of spastic paraparesis or paraplegia?

A. As follows:
- MND (e.g. amyotrophic lateral sclerosis)
- Subacute combined degeneration
- Transverse myelitis
- Multiple sclerosis
- Friedreich's ataxia
- Lathyrism
- Syringomyelia
- Vascular disease of the cord
- Hereditary spastic paraplegia
- Tropical spastic paraplegia
- Post-vaccination

- Syphilitic amyotrophy
- Non-metastatic manifestation of malignancy
- Radiation myelopathy
- Functional.

According to the type of lesion:

1. Demyelinating:
   - MS
   - ADEM.
2. Inflammatory:
   - Sarcoidosis
   - Postviral
   - Post-vaccinal.
3. Infective:
   - HIV
   - Herpes zoster
   - Herpes simplex
   - Syphilis.
4. Degenerative:
   - MND (Motor nuron disease)
   - FSP (Familial spastie paraplegia)
   - SCD (Spinocerebellar degeneration)
   - FA (Friedrelen's ataxia).
5. Vascular:
   - Anterior spinal artery occlusion
   - Intramedullary hemorrhage
   - Spinal AVM.
6. Toxic:
   - Lathyrism
   - Radiation.

Q. What are the **causes of paraplegia of sudden onset?**

A. As follows:

- Trauma (to vertebral column)
- Collapse of vertebra due to any cause
- Acute transverse myelitis
- Multiple sclerosis
- Anterior spinal artery thrombosis
- Post-vaccination myelitis
- Dissecting aneurysm
- Hematomyelia (due to arteriovenous malformation or angioma).

Q. What is **paraplegia in flexion** and **paraplegia in extension**?

A. Paraplegia in extension and paraplegia in flexion follows severe injury to the spinal cord.

- Paraplegia in extension: It indicates an increase in the extensor muscle tone leading to an extension attitude of the lower limbs (hip and knee extended, feet plantar flexed), due to involvement of pyramidal tracts as a result of partial transection of spinal cord, but the extrapyramidal tracts (specially vestibulospinal tracts) are intact. It may change to paraplegia in flexion if the damage to the spinal cord becomes more extensive and the vestibulospinal tracts are destroyed.

- Paraplegia in flexion: Here lower limbs take a flexion attitude (the limbs are involuntarily flexed in hips and knees, feet are dorsiflexed). It is due to complete transection of spinal cord. Here both pyramidal and extrapyramidal tracts are affected.

Differences between Paraplegia in extension and Paraplegia in flexion:

	Paraplegia in extension	Paraplegia in flexion
1. Cause	Pyramidal lesion	Pyramidal and extrapyramidal
2. Hypertonia	More in extensors	More in flexors
3. Position of lower limbs	Extended	Flexed
4. Deep reflexes	Exaggerated	Less exaggerated
5. Clonus	Present	Absent
6. Mass reflex	Absent	May be present
7. Bladder	Precipitancy	Automatic bladder

Q. What is **mass reflex?**

A. Following stimulation of skin of the lower limbs or lower abdominal wall, there is reflex flexion of the lower trunk muscles and the lower limbs, evacuation of the bladder, bowel and semen and sweating, called mass reflex. This reflex indicates severe spinal cord lesion.

Q. What are the causes of **absent ankle jerk**, but **extensor plantar** response?

A. As follows:

- Subacute combined degeneration of the spinal cord
- Friedreich's ataxia
- Taboparesis
- Diabetes mellitus (DM) with cervical myelopathy
- Multiple sclerosis.

Q. How to **find out** the sensory level in spinal cord compression?

A. In the following ways:

Vertebral level	Spinal cord segment
1. Cervical vertebrae	Add 1
2. Upper thoracic vertebrae (T1 to T6)	Add 2
3. Mid thoracic vertebrae (T7 to T9)	Add 3
4. 10th thoracic vertebra	Lumbar 1 and 2
5. 11th thoracic vertebra	Lumbar 3 and 4
6. 12th thoracic vertebra	Lumbar 5
7. First lumbar vertebra	Sacral and coccygeal cord segments

Q. What are the **findings** of spinal cord compression at different levels of spinal cord?

A. As follows:

- **Lesion above C_5**—UMN lesion in both upper and lower limbs with loss of sensation in all four limbs.
- **Lesion at C_5**—LMN lesion in proximal muscles of upper limbs (rhomboid, deltoid, biceps, brachioradialis) with segmental loss of sensation and UMN lesion in rest of the upper limbs and in lower limbs. Biceps reflex is lost and triceps jerk is exaggerated.
- **Lesion at C_8**—LMN lesion and wasting of the intrinsic muscles of the hand and UMN lesion in lower limbs. There is segmental loss of sensation.
- **Lesion in thoracic cord**—Spastic paraplegia with segmental sensory loss. (Loss of upper abdominal reflexes at T_7 and T_8. Loss of lower abdominal reflexes and upward displacement of the umbilicus at T_{10} and T_{11}).
- **Lesion at L_1**—UMN lesion in lower limbs and cremasteric reflex is lost (normal abdominal reflex).
- **Lesion at L_4**—LMN lesion and wasting of quadriceps, loss of knee jerk but hyperreflexia of ankle jerk and extensor plantar response.
- **Lesion in L_5 and S_1**—LMN weakness of knee flexion and hip extension (S_1) and abduction (L_5) and calf and foot muscles. Knee jerk is present, but no ankle jerk or plantar response. Anal reflex is present.
- **Lesion in S_3 and S_4**—No anal reflex, saddle sensory loss, normal lower limbs.

Note Remember to diagnose the cause of spastic paraplegia:

- If spastic paraplegia with sensory loss with a definite upper limit—diagnosis is **spinal cord compression**
- If plantar response is extensor, sensory loss in glove and stocking pattern, loss of vibration and position sense—diagnosis is **SCD**
- If presence of cerebellar signs—diagnosis is **MS** or **Friedreich's ataxia**
- In young patient with pes cavus, dorsal column lesion and cerebellar signs—diagnosis is **Friedreich's ataxia**
- If spastic paraplegia, but no sensory loss—diagnosis is **MND** (amyotrophic lateral sclerosis, also LMN lesion in upper limb).

Q. What are the causes of **flaccid paraplegia**?

A. As follows:

1. With bowel bladder involvement:
   - Spinal shock
   - Cauda equina syndrome.
2. Without bowel bladder involvement:
   - MND
   - Neuropathy—GBS and any other motor neuropathy involving the lower limb, AIDP
   - Periodic paralysis due to hyperkalemia or hypokalemia
   - Guillain-Barré syndrome (GBS)
   - Motor neuropathy due to any cause (such as acute intermittent porphyria, Charcot-Marie-Tooth disease, chronic lead poisoing, paraneoplastic syndrome)
   - Progressive muscular atrophy (MND)
   - Acute inflammatory demyelinating polyradiculopathy (AIPD)
   - Tabes dorsalis
   - Friedreich's ataxia
   - UMN lesion in shock stage

- Peripheral neuropathy involving both lower limbs
- Hysterical conversion reaction (HCR).

Note Remember the following:

Common causes of flaccid paraplegia are GBS and peripheral neuropathy.

Q. What are the causes of **hypotonia**?

A. As follows:

- LMN lesion due to any cause
- UMN lesion in shock stage
- Cerebellar lesion (knee jerk may be pendular)
- Dorsal column lesion (e.g. tabes dorsalis)
- Polyneuropathy
- Chorea (it is the only extrapyramidal lesion with hypotonia)
- Hypokalemia or hyperkalemia
- Down's syndrome
- Drugs like hypnotics, sedatives, muscle relaxants, anesthetics.

Q. What are the causes of **hypertonia**?

A. As follows:

- UMN lesion (spastic, may be clasp knife)
- Extrapyramidal lesion (lead pipe or cogwheel rigidity), except chorea
- HCR (rigidity continue to increase with more and more passive movement)
- Others—tetanus, strychnine poisoning, tetany, catatonic states
- Myotonia during the contraction phase
- Decerebrate rigidity (there is marked contraction of all extensor muscles in the body).

Q. What is the **difference** between rigidity and spasticity?

A. As follows:

- Spasticity means increased resistance during the initial part of passive movement, followed by lessening of the resistance. It may be clasp-knife type where the initial resistance is followed by sudden loss of resistance. It is due to pyramidal lesions. Spasticity is better felt with attempting extension of upper limbs and flexion of lower limbs. It is associated with other signs of UMN lesion. It involves only the anti-gravity muscles (extensors of the upper limbs and flexors of the lower limbs).
- Rigidity means sustained resistance during passive movement. It may be lead pipe in which resistance is uniform throughout the passive movement (better seen in elbow and knee) or cog wheel in which continuous resistance is interrupted by tremor (better seen in the wrist joint). Rigidity is found in extrapyramidal lesion. It involves all groups of muscles.

TRANSVERSE MYELITIS

CHIEF COMPLAINTS

- Sudden inability to walk for … days
- Inability to void urine for … days.

HISTORY

History of present illness: According to the statement of the patient, he was reasonably well one week ago. Since then, he has been suffering from low grade continued fever, which is not associated with chill and rigor and does not subside with sweating. For the last 3 days, suddenly he felt weakness in both of his lower limbs and was unable to walk. After that, he is completely bedridden and is unable to void urine and also unable to pass stool. He also complains of moderate pain along the lower part of his chest. There is no history of trauma, generalized bodyache or vaccination. There is no complaint regarding his upper limbs. Other systemic enquiry revealed normal.

History of past illness

Drug and treatment history

Personal history

Socioeconomic history

Family history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient is ill looking, anxious and bed ridden
- Mildly anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- Urinary catheter in situ
- Pulse: 72/min
- BP: 120/70 mm Hg
- Temperature: Normal
- Respiration: Normal.

SYSTEMIC EXAMINATION

Nervous System

1. **Higher cerebral functions:** Intact
2. **Cranial nerves including fundoscopy**: Intact
3. **Motor system:**
   - Muscle tone—increased in both lower limbs, normal in both upper limbs
   - Muscle power—diminished (grade 0/5) in both lower limbs, normal in both upper limbs
   - Wasting—absent
   - Reflexes:

Jerks	Biceps	Triceps	Supinator	Knee	Ankle	Plantar
Right	Normal	Normal	Normal	Exaggerated	Exaggerated	Extensor
Left	Normal	Normal	Normal	Exaggerated	Exaggerated	Extensor

- Coordination—normal
- Rombergism—could not be evaluated
- Gait—could not be evaluated
- Involuntary movement—absent

4. **Cerebellar function:** Intact
5. **Sensory system:** Sensory perception of all modalities is impaired below 10th thoracic dermatome and intact above it. There is some paresthesia along T_{10} dermatome.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 40 years old, businessman, normotensive, nondiabetic, nonsmoker, hailing from …, presented with low grade continued fever for 1 week. The fever is not associated with chill and rigor and does not subside with sweating. For the last 3 days, suddenly he felt weakness in both of his lower limbs and became unable to walk. Thereafter, he is completely bedridden and is unable to void urine and also unable to pass stool. He also complains of moderate pain along the lower part of his chest. There is no history of weight lifting, low back pain, trauma, generalized body ache or vaccination. There is no complaint regarding his upper limbs. Other systemic enquiry revealed normal.

There is no history of such illness in his family. He was treated by a local physician who referred him for immediate hospitalization.

On examination
General examination (mention as above)
Systemic examination (mention as above).

My diagnosis is spastic paraplegia, more likely due to acute transverse myelitis.

Q. What are your **differential diagnoses?**

A. As follows:

- Multiple sclerosis
- Subacute combined degeneration of spinal cord
- Trauma (to vertebral column)
- Collapse of vertebra due to any cause (metastasis, osteoporosis, TB)
- Anterior spinal artery thrombosis
- Post-vaccination myelitis
- Hematomyelia.

Q. Why is it **transverse myelitis**?

A. Because:

- Previous history of fever
- Followed by acute onset of spastic paraplegia
- Sensory loss in both lower limbs with sharp upper margin
- Involvement of bladder function
- No history of trauma, vascular incident, etc.

Q. What **investigations** should be done?

A. As follows:

- CBC (leukocytosis in systemic inflammation and infection)
- X-ray of the dorsolumbar spine (to exclude other cause)
- CSF study (protein high, lymphocyte high)
- CT scan and MRI of brain and spinal cord, depending upon site of leison.

RELATED QUESTIONS AND ANSWERS

Q. What is **transverse myelitis (TM)?**

A. It is the acute inflammatory, demyelinating disorder of the spinal cord causing paraparesis or paraplegia, or sometimes quadriplegia. It is usually secondary to viral infection, multiple sclerosis or other inflammatory and vascular disease.

Q. What are the **causes** of TM?

A. As follows:

1. **Traumatic**
2. **Infection:**
   - Viral—coxsackie, polio, EBV, herpes virus, HIV
   - Bacterial—pyogenic, tuberculous, syphilitic (rare)
   - Others—parasitic, fungal, schistosomiasis
3. **Vascular**—arteritis, anterior spinal artery occlusion
4. **Nutritional myelopathy**
5. **Miscellaneous**—postinfectious or postvaccinal inflammation, ADEM, multiple sclerosis, sarcoidosis, neuromyelitis optica
6. **Collagen vascular disease** (SLE, Sjogren syndrome, MCTD)
7. **Idiopathic.**

Q. What is the common **site** of transverse myelitis?

A. Mid thoracic region.

Q. What are the **features** of transverse myelitis?

A. Occurs in any age, follows viral illness or vaccination:

- Onset within hours to days, usually bilateral
- Fever may be present and acute or subacute onset of paralysis or paraparesis associated with back pain
- At the level of lesion, girdle constriction with hyperesthesia just above the lesion may be present
- Usually there is no root pain, spinal tenderness or spinal deformity
- The patient complains of urinary problem like retention, incontinence as bladder involvement is early
- There is partial or complete sensory loss, with a definite upper level
- MRI should be done to exclude compressive lesion
- Lumbar puncture and CSF study shows high protein and lymphocyte. Often there is high polymorph at the onset
- Outcome is variable. In some cases, near complete recovery occurs, despite severe initial deficit. Some patients go to develop multiple sclerosis in later years.

Q. How to **treat** TM?

A. As follows:

1. **General measures:**
   - Reassurance and psychological support
   - Care of bowel (manual evacuation may be necessary)
   - Care of bladder (catheterization)
   - Care of skin (to prevent bedsore)
   - Passive physiotherapy
   - Spasticity may be helped by baclofen, diazepam, tinazidine or botulinum toxin
   - Rehabilitation.
2. Treatment of specific cause, if any.
3. In patient with severe and rapidly progressive disease, initial empirical treatment usually includes administration of high dose glucocorticoid and IV acyclovir, while definite diagnostic tests are pending.
4. **Plasmapheresis**—those who do not respond to medicine.

MYOPATHY

CHIEF COMPLAINTS

- Weakness for … months
- Wasting of muscles for … months.

HISTORY

History of present illness: According to the statement of the patient, he was reasonably well … months back. Since then, he has been suffering from generalized weakness. Initially, he was feeling weakness of the upper limbs for which he was unable to raise his arms above head and feels difficulty in combing. For the last … months, he also experiences weakness of both lower limbs for which he feels difficulty in standing from sitting position and climbing stairs. It is not related to any physical exercise or activity, no diurnal variation and no muscular pain. He also complains of gradual wasting of muscles, initially of the upper limbs and then lower limbs. There is no history of fever, skin rash, tingling and numbness, sensory loss or involuntary movements, breathlessness, palpitaion, bowel or bladder abnormality. Other systemic enquiry revealed no abnormality.

History of past illness

Drug and treatment history

Personal history

Socioeconomic history: Mention according to the patient's statement

Family history: There is no history of consanguinous marriage among the parents.

GENERAL EXAMINATION

- Ill looking and emaciated
- Mildly anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- Pulse: 72/min
- BP: 120/70 mm Hg
- Temperature: Normal
- Respiration: Normal.

SYSTEMIC EXAMINATION

Nervous System

1. **Higher psychic functions:** Intact
2. **Cranial nerves:** Intact
3. **Motor system:**
   - Muscle tone—diminished in both upper and lower limbs
   - Muscle power—reduced (grade 3/5) in proximal muscles of all four limbs, and 5/5 in other group of muscles
   - Gower's sign is positive

- Wasting of shoulder and upper arm muscles
- Reflexes:

Jerks	Biceps	Triceps	Supinator	Knee	Ankle	Plantar
Right	Normal	Normal	Normal	Normal	Normal	Flexor
Left	Normal	Normal	Normal	Normal	Normal	Flexor

- Coordination—could not be performed due to weakness
- Rombergism—absent
- Gait—wadling gait
- Involuntary movement—absent

4. **Cerebellar functions:** Intact
5. **Sensory system:** Intact.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 19 years old, student, normotensive, nondiabetic, nonsmoker, hailing from …, presented with generalized weakness for … months. Initially, he was feeling weakness of the upper limbs for which he is unable to raise his arms above head and feels difficulty in combing. For the last … months, he also experiences weakness of both lower limbs for which he feels difficulty in standing from sitting position and climbing stairs. It is not related to any physical exercise or activity, no diurnal variation and no muscular pain. He also complains of gradual wasting of muscles, initially of the upper limbs and then lower limbs. There is no history of fever, skin rash, tingling and numbness, sensory loss or involuntary movements, breathlessness, palpitation, bowel or bladder abnormality. Other systemic enquiry revealed no abnormality. There is no history of similar illness in his family. He was treated with multiple vitamins and calcium tablets by local physicians.

On examination
General examination (mention as above)
Systemic examination (mention as above).

My diagnosis is myopathy, more likely limb girdle muscular dystrophy.

Q. Why it is myopathy?

A. Because:

- Gradual onset of symmetrical proximal muscle weakness such as difficulty in standing, difficulty in raising arms above head and difficulty in combing hair
- Tendon reflexes are normal
- No sensory loss.

All indicate muscular, not neurological problem.

Q. Why not neuropathy?

A. Because:

- In neuropathy, usually there is peripheral involvement
- The patient will complain of paresthesia, tingling and numbness
- In sensory neuropathy, there will be loss of sensation and reflexes
- In motor neuropathy, there is loss of reflex
- Onset is acute or subacute.

Q. What are your **differential diagnoses?**

A. As follows:

- Malnutrition (vitamin D deficiency)
- Tuberculosis
- Diabetes mellitus
- Thyrotoxicosis
- Hypoparathyroidism
- Other myopathy like facio-scapulo-humeral dystrophy, Duchenne muscular dystrophy, Becker's muscular dystrophy, etc.
- Drugs (zidovudine, statin, alcohol).

Q. What are the **causes** of emaciation or cachexia?

A. As follows:

- Tuberculosis
- Diabetes mellitus
- Thyrotoxicosis
- Malabsorption or malnutrition
- Malignancy
- Anorexia nervosa in young female
- Any chronic debilitating disease
- HIV infection.

Q. What **investigations** should be done in myopathy?

A. As follows:

- Creatine phosphokinase (CPK) is very high, up to 40-fold in Duchenne type (in other types, slightly raised)
- EMG shows short duration, low amplitude spiky polyphasic action potential (spontaneous fibrillation is also seen occasionally), reduction in motor unit amplitude and duration with normal number of units activated during effort
- ECG (cardiomyopathy and dysrhythmia), echocardiography, blood sugar
- Muscle biopsy (shows variation of muscle fiber size, degenerative changes, regeneration and replacement by fat. On immunological staining, there is absence of dystrophin. This is commonly found in Duchenne muscular dystrophy)
- Lactic acid (to exclude mitochondrial myopathy)
- Molecular genetic testing.

Q. What are the **differences** between neuropathy and myopathy?

A. As follows:

- Myopathy usually involves proximal muscles (except myotonia dystrophica, which involves distal muscles)
- Neuropathy usually involves distal muscles (except diabetic amyotrophy), GBS, amyloidosis, Lyme disease.

RELATED QUESTIONS AND ANSWERS

Q. What is **myopathy?**

A. It means disease of the skeletal muscle (voluntary) muscle.

Q. What is **muscular dystrophy**? What are the **types** of muscular dystrophy?

A. It is a group of hereditary muscular disorder characterized by progressive degeneration of groups of muscles without the involvement of nervous system with absence or reduced dystrophin. The types are:

1. **Hereditary muscular dystrophy:**
   - Duchenne type (pseudohypertrophic)
   - Becker muscular dystrophy
   - Limb girdle myopathy
   - Fascio-scapulo-humeral dystrophy
   - Myotonia dystrophica
   - Myotonia congenita
   - Others are oculopharyngeal or ocular myopathy, and congenital muscular dystrophy.
2. **Congenital myopathy (rare):**
   - Central core
   - Nemaline myopathy
   - Myotubular myopathy.
3. **Secondary myopathy** (such as endocrine disease and drugs).

Q. What is **Duchenne muscular dystrophy?** What are the **features**?

A. It is inherited as X-linked recessive disorder (30% spontaneous mutation). Duchenne gene is on the short arm of X-chromosome, Xp21 and its product called dystrophin is absent (diagnosed by western blot analysis of muscle biopsy).

- Affects only male, age of onset 3 to 4 years
- The child presents with difficulty in walking or getting up from sitting or lying position. There is history of frequent fall and delayed motor activity (e.g. walking)
- Gower's sign is positive (while the child gets up from lying position, he uses the hands to climb up)
- There is pseudohypertrophy in early stage involving calf and deltoid muscles. Later, there is weakness, first involves the proximal muscles
- Gait-waddling (duck like)
- Other features include dilated cardiomyopathy, kyphoscoliosis and mental retardation. There is early respiratory involvement
- Prognosis is poor, chair bound by the age of 10 years and few survive up to 20 years
- Causes of death are dilated cardiomyopathy and respiratory failure or inanition.

Q. What is **Becker muscular dystrophy**?

A. It is inherited as X-linked disorder, only males are affected and features are same as Duchenne type with the exception of:

- Onset is late (5 to 25 years)
- Less severe, less rapid progression and less incidence of cardiomyopathy. Mental retardation and kyphoscoliosis are uncommon. Respiratory involvement is a late feature
- Chair bound at about 25 years after the onset
- Survival—fourth to fifth decade.

Causes of pseudohypertrophy of calf muscles:

- Duchenne muscular dystrophy
- Becker muscular dystrophy.

Q. What is **limb girdle myopathy**?

A. It is a type of muscular dystrophy, inherited as an autosomal dominant (type 1)—10% and autosomal recessive (type 2)—90%, characterized by the involvement of shoulder and pelvic girdle muscles

- Age of onset is 10 to 30 years, male and female are equally affected
- May involve cardiac muscle (may cause conduction abnormality or heart failure)
- Intelligence is normal, face is normal, muscle enzymes are normal or slightly elevated
- Prognosis is poor, chair-bound at 20 to 25 years of age (10 to 20 years after the onset of disease).

Q. What is **fascio-scapulo-humeral dystrophy**? What are the **features**?

A. It is a type of muscular dystrophy, inherited as an autosomal dominant, characterized by the involvement of muscles of the face and shoulder girdle.

- Onset is 10 to 40 years of age
- Course is variable, but usually relatively benign
- There is wasting of muscles of face, neck and shoulder girdle (lower trapezzi, pectoralis, biceps, triceps). Hypertrophy of the deltoid
- Winging of scapula (due to the involvement of serratus anterior muscle)
- Pain in shoulder girdle is common
- Face looks dull, expressionless, lips open and slack, inability to whistle and puff the cheek
- Eyes—bilateral partial ptosis
- There may be distal lower limb weakness
- Intelligence is normal
- Prognosis—normal life span, and slowly progressive
- Muscle enzymes are usually normal or slightly elevated
- Inflammatory and perivascular inflammation may be seen in muscle biopsy. Also, retinal microvascular abnormality may be found.

Q. What is **myotonia?** What are the **causes?**

A. It is the continued contraction of the muscles with slow relaxation after cessation of voluntary contraction. Causes are:

- Myotonia dystrophica
- Myotonia congenita (Thomsen's disease)
- Others—hyperkalemic periodic paralysis, myxedema (Hoffman's syndrome), hereditary paramyotonia (autosomal dominant), cold-induced myotonia and drug (clofibrate).

Note Remember the following:

Patients with myotonia tolerate anesthesia poorly

Q. How to **elicit** myotonia?

A. As follows:

- The patient is asked to close the hands tightly. If asked to open, it relaxes slowly. Same thing happens if asked to close the eyes, which opens slowly
- Inability to relax hands after handshake (grip myotonia)
- Percussion over the thenar eminence with fingers produces dimples or depressions, which fill up slowly (percussion myotonia). Similar percussion over the tongue produces same finding.

Q. What is **myotonia congenita?**

A. It is an inherited disorder (autosomal dominant), characterized by failure to relax the muscle after forceful contraction. Present at birth with feeding difficulty, inability to open the eyes and a peculiar

cry. It is a mild disease, improves with age. Other features of myotonia dystrophica are absent. There may be diffuse muscular hypertrophy due to continuous involuntary isometric contraction.

Treatment of myotonia—procainamide, quinidine, mexiletine may be helpful
Prognosis—normal life expectancy.

Q. What are the features of **myotonia dystrophica?**

A. As follows:

1. **In face:**
   - Frontal baldness (patient may be wearing wig)
   - Long, lean, triangular, sad and expressionless face (hatchet facies)
   - Wasting of temporalis and masseter.
2. **Eyes:**
   - Partial ptosis (usually bilateral, may be unilateral) with smooth forehead
   - Cataract (stellate cataract). May be subcapsular fine deposit
   - Difficulty in opening the eyes after firm closure.
3. **Neck**—wasting of sternomastoid and shoulder girdle muscles. There is weakness of flexion and normal extension.
4. **Hands:**
   - The patient is asked to close the hands tightly, which relaxes slowly if asked to open
   - Inability to relax hands after handshake
   - Percuss on thenar eminence with fingers. There are dimples or depressions, which fill up slowly.
5. **Others:**
   - Percussion may be done on the tongue (dimples or depressions are seen)
   - Wasting of distal muscles of arms (forearm wasting first) and legs
   - Testes (atrophy)
   - Gynecomastia
   - Heart (cardiomyopathy and conduction defect).

Other features of myotonia dystrophica:

- Inherited as autosomal dominant
- Males are affected more than females
- Age of onset may be any (usually 20 to 50 years)
- Diabetes mellitus and impaired glucose tolerance (IGT) may occur
- Intellect and personality may have mild deterioration
- Small pituitary fossa and hypogonadism may occur
- Low serum IgG levels
- Tolerate anesthesia poorly.

Q. What are the **EMG findings of myotonia?**

A. High-frequency activity that varies repeatedly (waxing and waning of potentials), to cause a characteristic sound on loud speaker (called **Dive-Bomber effect).**

Q. What are the **EMG findings in myopathy?**

A. Short duration, spiky, polyphasic muscle action potential are seen. Spontaneous fibrillation is occasionally recorded.

Q. How to **treat** myotonia dystrophica?

A. Only symptomatic. No specific treatment.

- Myotonia may be treated by phenytoin (procainamide or quinidine may be used, but may worsen cardiac conduction)
- Genetic counselling

Q. What are the **causes** of proximal myopathy?

A. As follows:

- Dermatomyositis or polymyositis
- Myasthenia gravis
- Myasthenic myopathic syndrome (Eaton–Lambert syndrome)
- Myopathy (limb girdle, fascio-scapulo humeral and mitochondrial), except myotonic dystrophy
- Cushing's syndrome
- Diabetic amyotrophy
- Thyrotoxicosis (also hypothyroidism)
- Polymyalgia rheumatica
- Osteomalacia
- Hyperparathyroidism
- Periodic paralysis
- Alcohol and drugs (steroid, chloroquine, amiodarone, lithium and zidovudine)
- McArdle's syndrome (myophosphorylase deficiency, there is stiffness and cramps of muscle after exercise, which is hard and painful on movement).

Q. What are the causes of **distal** muscle weakness?

A. As follows:

- Myotonic dystrophy
- Charcot-Marie-Tooth disease
- Peripheral neuropathy (except diabetic amyotrophy)
- Distal myopathy.

Q. What are the **causes of painful muscle**?

A. As follows:

- Physiological (after exercise)
- Polymyositis or dermatomyositis
- Polymyalgia rheumatica
- Fibromyalgia syndrome
- Viral infection
- Chronic alcoholism
- Hypoparathyroidism
- Vitamin D deficiency
- Following convulsion
- Associated with rheumatological disease
- Functional.

Q. What are the **causes of acute** or **sudden muscular weakness**?

A. As follows:

- Guillain-Barré syndrome
- Hypokalemia and hyperkalemia
- Familial periodic paralysis
- Thyrotoxic periodic paralysis
- Functional (hysterical conversion reaction, HCR).

Q. What are the **drugs** causing myopathy?

A. Steroid, penicillamine, hydroxychloroquine or chloroquine, statins (lovastatin), zidovudine and clofibrate (also alcohol and cocaine cause myopathy).

Q. What are the causes of **high CPK?**

A. As follows

- Exercise
- Intramuscular injection
- Muscle trauma or road traffic accident
- Convulsion
- Alcoholism
- Dermatomyositis or polymyositis
- Acute myocardial infarction (CPK-MB)
- Myopathy (Duchenne type of muscular dystrophy)
- Rhabdomyolysis
- Chronic liver disease (CLD)
- Drugs include statins, busulphan, narcotics, colchicine and chloroquine
- Neuroleptic malignant syndrome
- Malignant hyperthermia.

Note Remember the following:

CPK is normal in myasthenia gravis, Eaton-Lambert syndrome and usually normal in myotonia (myotonic dystrophy)

Q. What are the CPK normal myopathies?

A. As follows:

- Facioscapulohumeral myopathy
- Scapulo-peroneal myopathy
- Distal myopathy (mostly)
- Zidovudine induced myopathy.

Iso-enzymes of CPK:

- MM (mainly in skeletal muscle)
- MB (mainly in cardiac muscle)
- BB (in brain).

WILSON'S DISEASE

CHIEF COMPLAINTS

- Tremor of hands and difficulty in writing for … months
- Difficulty in speech for … days
- Involuntary movements of hands and other parts of the body for … days.

HISTORY

History of present illness: The patient says that he was reasonably well … months ago. Since then he is complaining of tremor of both hands and difficulty in writing. It is aggravated on attempted movement and relieved by rest. It is gradually progressive and hampering his daily activities. He also complains of difficulty in speech for last … days. His mother stated that she noticed involuntary movements of hands and feet which are repetitive, semi purposive and is absent during sleep. His intellect is average and there had been no deterioration of his academic performance. There is no history of fever, weight loss, convulsion, head trauma or unconsciousness. His bowel and bladder habits are normal.

History of past illness: He suffered from three episodes of jaundice in his early childhood, with spontaneous recovery from each episode.

Family history: There is history of consanguineous marriage among his parents. There is no history of such illness in his family.

Drug history: He was treated by local physicians by multiple drugs, the name of which he cannot mention.

Personal history: He is a student of class 10, he is from a middle class family.

GENERAL EXAMINATION

- Appearance: Anxious
- Anemia, jaundice, cyanosis, clubbing, koilonychia, leuconychia, edema, dehydration—absent
- No thyromegaly or lymphadenopathy
- Pulse: 72/min
- BP: 100/60 mm Hg
- Temperature: Normal.

SYSTEMIC EXAMINATION

Neurological Examination

1. **Higher cerebral function:** Normal
2. **Speech:** Scanning
3. **Cranial nerves including fundoscopy:** Normal except presence of horizontal nystagmus
4. **Examination of the eyes:** KF ring present in both eyes, on the left eye at 11 o'clock position and in right eye on 10 o'clock position
5. **Motor function:** Intact except hypotonia in all four limbs and fine tremor of outstretched hand. Gait is ataxic

6. **Sensory function:** Intact.
7. **Cerebellar function:**
   - Horizontal nystagmus
   - Scanning speech
   - Intention tremor with past pointing
   - Hypotonia.

Examination of other systems reveals normal findings.

SALIENT FEATURE

Mr …, 14 years of age, student, right handed boy, hailing from …, presented with tremor of both hands and difficulty in writing for … months. It is aggravated on attempted movement and relieved by rest. It is gradually progressive and hampering his daily activities. He also complains of difficulty in speech for last … days. His mother stated that she noticed involuntary movements of hands and feet which are repetitive, semi-purposive and is absent during sleep. His intellect is average and there had been no deterioration of his academic performance. There is no history of fever, weight loss, convulsion, head trauma or unconsciousness. His bowel and bladder habits are normal. He suffered from three episodes of jaundice in his early childhood, with spontaneous recovery from each episode. There is history of consanguineous marriage among his parents. There is no history of such illness in his family. He was treated by local physicians by multiple drugs, the name of which he cannot mention.

On examination
General examination (mention as above)
Systemic examination (mention as above).

My diagnosis is wilson's disease

Q. Why Wilson's disease?

A. Because, there is history of previous hepatitis, involuntary movement, cerebellar sign and presence of KF ring. All are suggestive of Wilson's disease.

Q. What are your **differential diagnoses?**

A. As follows:
- Cerebellitis
- Drug induced cerebellar syndrome
- Post-encephalitic syndrome.

Q. What is **KF ring?**

A. It is greenish brown pigmentation at the sclerodermal junction due to deposition of copper in the Decimet's membrane of the cornea, occasionally seen by slit lamp examination. May be absent or less in young children but always present in neurological Wilson's disease.

Q. What are the causes of **KF ring?**

A. As follows:
- Wilson's disease
- Primary billiary cirrhosis
- Chronic active hepatitis with cirrhosis
- Cryptogenic cirrhosis
- Long-standing intrahepatic cirrhosis of childhood.

Q. What investigations should be done in Wilson's disease?

A. As follows:

- Serum ceruloplasmin—low
- Serum-free copper—high
- 24 hours urinary copper—high (normal <40 mg, in Wilson's disease—100 to 1000 mg or 0.6 mmol/24 h)
- 24 hours urinary copper following penicillamine therapy >25 mmol is a confirmatory test
- Liver biopsy with quantitative measurement of copper (high hepatic copper, usually not done).

RELATED QUESTIONS AND ANSWERS

Q. What is Wilson's disease? What is the **primary defect**?

A. Wilson's disease is an inborn error of copper metabolism, inherited as autosomal recessive trait, characterized by failure of biliary excretion of copper and its deposition in and damage of different organs such as liver, brain, eye, kidney, bone, etc. There is more absorption of copper from the small intestine but less excretion by liver. Ceruloplasmin production is less due to unknown mechanism.

Q. What are the **manifestations** of Wilson's disease?

A. Usually commonly in patients 5 to 30 years. In early age, usually hepatitis and in adult usually neurological features are common. Features are as follows:

1. **Hepatic:**
   - Acute or chronic hepatitis, often recurrent manifested by attacks of jaundice
   - Eventually, multilobular cirrhosis
   - Rarely, cirrhosis alone
   - Hepatic abnormality may be asymptomatic with only elevated transaminases
   - Unexplained hepatosplenomegaly
   - Hypersplenism with thrombocytopenia and bleeding
   - In severe hepatic failure, hemolytic anemia.
2. **Renal:**
   - Acute tubulopathy with renal tubular acidosis
   - Nephrolithiasis
   - Microscopic hematuria
   - Fanconi syndrome—excretion of phosphates, amino acids, glucose or urates.
3. **Neurologic:**
   - Three main movement disorder: Dystonia, Incordination, Tremor (DIT)
   - Extrapyramidal manifestation: Parkinsonian syndrome (tremor, slowness of movement, rigidity, flexed limb postures), oropharyngeal abnormality (dysphagia, dysarthria, hoarseness), chorea, athetosis, dystonia
   - Cerebellar syndrome (ataxia and intention tremor)
   - Seizure (6%), dementia
   - Autonomic disturbance: Orthostatic hypotension, sweating abnormality, bowel, bladder and sexual dysfunction
   - No sensory abnormality.
4. **Eye:**
   - Kayser-Fleischer rings (commonly 10 to 12 o'clock position, in upper periphery)
   - Sun-flower cataracts (rare, due to deposition of copper in the lens).

5. **Psychiatric:**
   - Behavioral disturbances with onset 5 years before diagnosis occurs in half of the patient. They includes—loss of emotional control- temper tantrums, crying bouts, depression, hyperactivity, loss of sexual inhibition, gradual development of intellectual faculties.
6. **Others:**
   - Hemolytic anemia
   - Aminoaciduria or Fanconi syndrome
   - Osteoporosis
   - Cholelithiasis
   - Spontaneous abortion
   - Amenorrhea.

Q. How to **treat** Wilson's disease?

A. As follows:

1. **Penicillamine** (drug of choice, 1 to 3 g/day in divided dose with pyridoxine 25 mg/day to prevent anemia) or trientine. Treatment should be continued lifelong
2. **Zinc-acetate** (inhibits absorption of copper from GIT—ineffective alone)—100 to150 mg/day
3. **Liver transplantation** in fulminating hepatic failure or in advanced cirrhosis
4. **Symptomatic treatment:**
   - Dystonia—trihexyphenidyl/clonazepam/diazepam
   - Seizure—anti-epileptics
   - Psychosis—antipsychotic
5. **General measures**—reduction of dietary copper intake (< 1 mg/day)
   - Avoidance of copper rich foods—liver, mushrooms, beans, cocoa, chocolates, nuts, shelfish, colored leafy vegetables, red meat, organ meat—kidney, liver, brain, bone marrow.
   - Aviodance of copper containing drugs
   - Aviodance of copper containing vergetables.
6. **Premarital screening**. Avoid consanguineous marriage.
7. **Follow up**—clinical improvement of S/S with measurement of urinary copper.

Q. How to **treat** in pregnancy?

A. Same treatment should be given.

Q: What is the **prognosis** of Wilson's disease?

A: Prognosis is excellent, provided the treatment is started before irreversible damage. Sibling and children must be investigated and treatment should be given, even they are asymptomatic.

INTRACRANIAL SPACE OCCUPYING LESION (ICSOL)

CHIEF COMPLAINTS

- Buzzing in the left ear for … months
- Progressive deafness of left ear for … months
- Headache and facial pain on the left side for … months.

HISTORY

History of present illness: Miss …, 23 years, was apparently well … months back. Since then, she has been suffering from buzzing sounds in the left ear, which is gradually becoming worse day by day. It is associated with deafness in the same side for last … months. Initially it was mild, but gradually it became worse and now she cannot hear anything with her left ear. The patient also complains of left sided headache and pain in the left side of the face. The pain is dull in nature, intermittent, more marked in the morning after waking from sleep, not associated with nausea or vomiting. There is no history of fever, pain or any discharge form left ear, weight loss, convulsion, difficulty in walking or unconsciousness. Her bowel and bladder habits are normal.

History of past illness: Nothing contributory.

Drug History: Nothing contributory.

Family history: Nothing contributory.

Personal history: Nothing contributory.

Menstrual history: Regular flow at 28–30 days interval.

GENERAL EXAMINATION

- Appearance: Depressed, some flickering movement of face in left side
- Anemia, jaundice, cyanosis, clubbing, leuconychia, koilonychias, edema—absent.
- No thyromegaly or lymphadenopathy
- Pulse: 76/ min
- BP: 110/65 mm Hg
- Temperature: Normal.

SYSTEMIC EXAMINATION

Neurological Examination

1. **Higher cerebral function:** Normal.
2. **Speech:** Scanning.
3. **Cranial nerves including fundoscopy:**
   - 5th nerve—all modalities of sensation are diminished over the face on left side. Corneal reflex is absent, on left side
   - 6th nerve—impaired abduction of left eye and diplopia on movement of the left eye (image of finger is parallel)
   - 7th nerve—normal
   - 8th nerve—sensory neural deafness in left ear

- Palatal movement – slightly restricted on left side.
- Other cranial nerves are normal.
- Fundoscopy—bilateral early papilledema.

4. **Motor function:** Intact except hypotonia in all four limbs. Gait is normal.
5. **Sensory function:** Intact.
6. **Cerebellar function:**
   - Horizontal nystagmus
   - Scanning speech
   - Hypotonia.

Examination of other systems reveals normal findings.

SALIENT FEATURE

Miss …, 23 years, right handed, normotensive and non-diabetic, hailing from …, presented with buzzing sounds in the left ear for … months, which is gradually becoming worse day by day. It is associated with deafness in the same side for last … months. Initially it was mild, but gradually it became worse and now she cannot hear anything with her left ear. The patient also complains of left sided headache and pain in the left side of the face. The pain is dull in nature, intermittent, more marked in the morning after waking from sleep, not associated with nausea or vomiting. There is no history of fever, pain or any discharge form left ear, weight loss, convulsion, difficulty in walking or unconsciousness. Her bowel and bladder habits are normal. There is no family history of such illness. She was treated by local physicians with prochlorperazin, cinnarizine, paracetamol and vitamins but there was no response.

On examination
General examination (mention as above)
Systemic examination (mention as above).

With this history and physical findings, my clinical diagnosis is intracranial space occupying lesion, more likely acoustic neuroma.

Q. Why **acoustic nerumoa?**

A. Because, there is history of tinnitus and progressive deafness on left side. On examination, there are lesions involving 5th, 6th and 8th nerve and also cerebellar sign. All indicates lesion in cerebellopontine angle, acoustic neuroma is the most common cause.

Q. What is the other **CP angle tumor?**

A. Meningioma. (Cholesteatoma may give similar picture).

Q. Mention one **investigation** to confirm your diagnosis.

A. MRI of brain.

Q. What other investigations would you suggest in a suspected case of brain tumor?

A. As follows:

- CT scan with contrast
- Chest X-ray (to see any primary lesion, there may be secondaries in the brain)
- In suspected cases—CT scan of chest, abdomen and pelvis
- Bone scan
- CSF cytology for lymphoma, meningeal metastasis and ependymoma
- Biopsy (for confirmation).

RELEVANT QUESTIONS AND ANSWERS

Q. What are the **features** of raised intracranial pressure?

A. As follows:

1. **Symptoms:**
   - Headache (deep seated, dull aching, worse by exertion, coughing, bending forward, more marked in the morning after waking from sleep)
   - Impairment of consciousness, drowsiness, even coma
   - Vomiting (may be projectile, usually without nausea)
   - Convulsion (may be generalized or focal).
2. **Signs:**
   - Bradycardia
   - Arterial hypertension
   - Respiration—deep and slow
   - Fundoscopy shows papilledema
   - Bulged anterior fontanelle in infant.
3. **X-ray skull shows**—silver bitten appearance, sutural diastasis (in infants).

Q. What is **cerebello-pontine angle** (CP angle)?

A. CP angle is the area of lateral cistern containing CSF, arachnoid tissue, cranial nerves and their associated vessels. The borders of CP angle are:

- Medial border—lateral surface of the brainstem
- Lateral border—petrous bone
- Superior border—middle cerebellar peduncle and cerebellum
- Inferior border—arachnoid tissue of lower cranial nerves
- Posterior border—cerebellar pedunclue.

Q. What are the common tumors of the posterior fossa or cerebellopontine angle?

A. As follows:

- Acoustic neuroma (or vestibular schwannoma > 80%)
- Others—meningioma, epidermoid or dermoid cyst, 7th or 5th nerve neuromas, giant basilar aneurysm, cerebellar glioma, pontine glioma, nasopharyngeal tumor extension, metastatic tumors (very rare), etc.

CP angle tumors are the most common posterior fossa tumors. Majority are benign.

Q. What are the clinical features of CP angle tumor?

A. As follows:

- Combination of 8th, 7th, ophthalmic branch of 5th, with or without ipsilateral cerebellar signs, is the hallmark of CP angle lesion
- Common presenting features are ipsilateral hearing loss, tinnitus, vertigo, unsteadiness and sensory abnormality in face
- Features of raised intracranial pressure may be present
- There may be signs of brainstem compression, particularly contralateral hemiparesis
- May result in 9th and 10th nerve palsies when tumor is very large.

Q. What is acoustic neuroma?

A. Acoustic neuroma (or vestibular schwannoma) is a benign tumor of Schwann cells of the 8th cranial nerve. It may occur in isolation or as a part of neurofibromatosis type II where it is often bilateral and associated with other central neoplasms like meningioma, cerebral and optic nerve glioma, spinal neurofibroma, etc. and few or no cutaneous lesion. MRI is the investigation of choice to diagnose acoustic neuroma.

Treatment:

- Surgical excision
- Stereotactic radiosurgery is used to slow down or stop the tumor growth, not to cure or remove the tumor. Often performed in elderly or sick patients who are unable to tolerate brain surgery.

Q. Why headache in intracranial tumor?

A. Headache is due to raised intracranial pressure or due to the traction on the pain sensitive intracranial structures.

Q. What is the classification of intracranial tumors?

A. As follows:

1. **Malignant:**
   - Glioma (astrocytoma)
   - Oligodendroglioma
   - Medulloblastoma
   - Ependymoma
   - Cerebral lymphoma.
2. **Benign:**
   - Meningioma
   - Neurofibroma
   - Craniopharyngioma
   - Pituitary adenoma
   - Colloid cyst
   - Pineal tumors.

Q. What are the tumors of the pituitary region?

A. As follows:

- Pituitary adenoma—microadenoma (<1 cm) and macroadenoma
- Craniopharyngioma
- Optic nerve glioma
- Suprasellar meningioma.

Q. What are the common clinical features of intracranial mass lesions?

A. As follows:

- Local effects on adjacent brain tissue—seizures, focal signs (depends upon the localization of the tumors)
- Features due to raised ICP—headache, vomiting, papilledema, depressed level of consciousness
- False localizing signs—unilateral or bilateral sixth nerve palsy, ipsilateral hemiparesis, bilateral extensor plantar responses
- Others—mental changes, depression, fatigability.

Q. What are the common focal signs of intracranial tumors?

A. As follows:

1. **Frontal lobe:**
   - Contralateral face, arm or leg weakness
   - Expressive dysphasia (dominant hemisphere)
   - Personality change—antisocial behavior, loss of initiatives
   - Profound dementia.
2. **Parietal lobe:**
   - Disturbed sensation

- Visual field defect
- Right left confusion
- Finger agnosia
- Acalculia
- Agraphia
- Sensory or motor neglect.

3. **Temporal lobe:**
   - Receptive dysphasia
   - Visual field defect.
4. **Cerebellopontine angle tumors:**
   - Eighth nerve damage causing gradually progressive sensorineuronal deafness, vertigo, tinnitus
   - Fifth nerve damage causing facial pain, numbness and paresthesia, depression of corneal reflex is an important early sign
   - Ninth, 10th and 11th nerve damage occasionally causes swallowing difficulty, voice change and palatal weakness
   - Cerebellar and pontine damage causing ataxia, ipsilateral incoordination and nystagmus. Pontine damage may produce contralateral hemiparesis.
5. **Pituitary tumors:**
   - Hyper or hyposecretion of hormones
   - Stunted growth
   - Visual field defect
   - Headache.

Q. How to **treat** brain tumors?

A. As follows:

- Surgery
- Chemotherapy
- Radiotherapy.

CHAPTER 9

Endocrinology

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HYPOTHYROIDISM

CHIEF COMPLAINTS

- Weight gain and swelling of the whole body for … months
- Cold intolerance for … months
- Increased sleepiness, lethargy, anorexia and weakness for … months
- Constipation for … months
- Lack of concentration and poor memory for … months.

HISTORY

History of present illness: According to the statement of the patient, she was alright … months back. Since then, she is suffering from weight gain and generalized swelling of the whole body, which is progressively increasing in spite of her less appetite. The patient also complains of intolerance to cold and prefers warm environment. For the last … months, she feels very lethargic, extremely weak, generalized body ache and constipation. She also feels sleepiness during most of the time even during working hours, lack of concentration and disturbance of memory since the beginning of her illness. Recently, her voice has changed and become hoarse. She also noticed that her skin is rough and dry. There is no history of chest pain, palpitation, breathlessness, tingling, numbness of hands or feet or loss of consciousness.

History of past illness: There is no history of thyroid disease, thyroid surgery, radiation to the neck or drugs. She denies childbirth or difficult delivery (within the last 6 months).

Menstrual history: She complains of excessive menstrual bleeding for the last 3 months, though it was normal previously.

Family history: No such illness in her family. All the family members are alright.

Socioeconomic history: She is a housewife in a middle-class family.

Drug and treatment history: Prior to her present illness, she did not take any drugs. There is no history of taking any oral contraceptive pill. After the illness, she has only taken multivitamin tablets and iron tables prescribed by a local physician.

GENERAL EXAMINATION

- The patient looks pale and apathetic
- The whole body is swollen
- The face is coarse and puffy with periorbital swelling, baggy eye lids and loss of outer one-third of the eyebrows
- She is mildly anemic, but there is no jaundice, cyanosis, clubbing, koilonychia or leukonychia
- There is nonpitting edema
- Skin is dry, rough, cold and thick (There may be yellow skin due to carotenemia, vitiligo and erythema ab igne, mention if present)
- Thyroid gland—not enlarged (mention, if enlarged)
- Pulse—50/min, high volume
- BP—120/90 mm Hg

SYSTEMIC EXAMINATION

Cardiovascular System

- Pulse—50/min, regular, high volume, normal in character
- BP—120/90 mm Hg
- Neck veins—not engorged
- Precordium—no abnormality detected.

Central Nervous System (CNS)

- Higher psychic functions:
  - Speech—voice is coarse and husky (or croaky)
  - Memory—slightly impaired (may be normal).
- Motor functions:
  - Slow relaxation of the ankle jerks
  - (Evidence of carpal tunnel syndrome may be present, mention if any.)
- Sensory functions—intact.

Musculoskeletal System

- Muscle and joints—tender (may be normal).

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mrs. …, 35 years old, housewife, normotensive, nondiabetic, hailing from …, presented with the weight gain and generalized swelling of the whole body for … months, which is progressively increasing inspite of her less appetite. The patient also complains of intolerance to cold and prefers warm environment. For the last … months, she feels very lethargic, extremely weak, generalized body ache and constipation. She also feels sleepiness during most of the time even during working hours, lack of concentration and disturbance of memory since the beginning of her illness. Recently, her voice has changed and become hoarse. She also noticed that her skin is rough and dry. There is no history of chest pain, palpitation, breathlessness, tingling, numbness of hands or feet or loss of consciousness. She also complains of excessive menstrual bleeding for the last 3 months, although it was normal previously. There is no history thyroid disease, thyroid surgery, radiation to the neck or drugs. She denies childbirth or difficult delivery (within the last 6 months). She gives no history of taking drugs including oral contraceptive pills prior to her present illness. There is no family history of similar illness. She was treated with calcium tablet and vitamins.

On Examination

General examination—mention as above
Systemic examination—mention as above.

My diagnosis is hypothyroidism (myxedema).

Q. What is the **difference** between myxedema and hypothyroidism?

A. Myxoedema is always associated with hypothyroidism, due to deposition of mucopolysaccharide substances, but all hypothyroidism may not be associated with deposition of mucopolysaccharide

substances, so may not be associated with myxedema. (In secondary hypothyroidism, there is no myxedematous change).

Q. What are your **differential diagnoses?**

A. As follows:

- Nephrotic syndrome
- Cushing's syndrome.

Q. Why not this is **nephrotic syndrome**?

A. In nephrotic syndrome, swelling usually starts at the face, later becomes generalized. Edema is pitting in nature. There is history of scanty micturition. All these are absent in this patient. On the other hand, the patient has cold intolerance, sleepiness, lack of concentration, non pitting edema and slow relaxation of ankle jerk and change of voice. These are not found in nephrotic syndrome.

Q. Why not **Cushing's syndrome**?

A. In Cushing's syndrome, there is central obesity along with relatively thin limbs. Other signs include plethoric moon face, buffalo hump, purple striae, etc. All these are absent in this patient (there may be history of prolong intake of steroid.)

Q. What do you think the **cause** in this case?

A. Spontaneous atrophic or autoimmune (because there is no goiter).

Q. If there is goiter with hypothyroidism, what is the **likely cause**?

A. Hashimoto's thyroiditis (Others – Graves' disease. In such case, there is exophthalmos).

Q. What **investigations** do you suggest in hypothyroidism?

A. As follows:

1. Serum FT_3, FT_4 and TSH (low FT_3, low FT_4 and high TSH).
2. Autoantibody (for Hashimoto's thyroiditis – antiperoxidase and antithyroglobulin antibody. However, if hypothyroid is associated with Graves' disease – TSH receptor antibody may be done).
3. Other routine tests:
   - CBC, ESR and PBF (there may be anemia, which is usually normocytic and normochromic, may be macrocytic anemia)
   - Ultrasonogram of the neck
   - ECG (low voltage tracing, sinus bradycardia)
   - X-ray chest (cardiomegaly due to pericardial effusion, heart failure)
   - Serum total cholesterol, LDL and triglyceride (high)
   - CPK, LDH, SGOT (all may be high—not done routinely).

Q. Tell one **single** investigation to diagnose hypothyroidism.

A. Serum TSH level.

Q. What are the **biochemical abnormalities** (other than thyroid hormones) in hypothyroidism?

A. As follows:

- Hypercholesterolemia and hypertriglyceridemia
- Hyponatremia (due to SIADH)
- High CPK and LDH
- Hyperprolactinemia.

Q. What is the **treatment of hypothyroidism**?

A. Thyroxine—it should be started with low dose. The dose should be increased gradually after three weeks. Single dose is preferable, should be taken before breakfast. TSH should be repeated after 6

to 8 weeks. Once TSH is normal, maintenance dose should be continued as a single daily therapy. For follow up—annual thyroid function test should be done.

Note. Remember the following -

If the patient has deficiency of cortisol (as in hypopituitarism or Addison's disease), corticosteroid should be given first and then thyroxine. Otherwise, if thyroxine is given first without correcting cortisol deficiency, there will be severe Addisonian crisis.

Q. Why **thyroxine** should be started in low dose?

A. Because if high dose is given, it may precipitate anginal attack.

Q. **How long** will you continue the treatment?

A. Life long.

Q. In hypothyroidism, if there is **no response** after thyroxine therapy, what are the possibilities?

A. As follows:

- Noncompliance or insufficient dose
- Associated hypopituitarism or Addison's disease
- Pernicious anemia.

RELATED QUESTIONS AND ANSWERS

Q. What are the **causes** of hypothyroidism?

A. As follows:

1. Autoimmune:
   - Spontaneous atrophic hypothyroidism
   - Hashimoto's thyroiditis
   - Graves' disease (associated with TSH receptor blocking antibody).

2. Iatrogenic:
   - Radioiodine therapy for thyrotoxicosis
   - After surgery (thyroidectomy)
   - Post-radiotherapy in neck
   - Drugs—such as lithium, amiodarone and antithyroid drug therapy.

3. Others:
   - Endemic iodine deficiency
   - Postpartum thyroiditis
   - Rarely, dyshormonogenesis
   - Secondary to hypopituitarism and hypothalamic disorders (rare).

Q. What are the causes of **goitrous** hypothyroidism?

A. As follows:

- Hashimoto's thyroiditis
- Graves' disease (in such case, there is also exophthalmos and diffuse goiter with dermopathy)
- Endemic iodine deficiency (less common)
- Drugs—lithium, amiodarone, iodide
- Rarely, dyshormonogenesis.

Q. What are the causes of **nongoitrous** hypothyroidism?

A. As follows:

- Autoimmune or idiopathic (spontaneous atrophic)—commonest cause
- Following radio-iodine therapy for thyrotoxicosis
- Post radiotherapy in the neck
- After surgery (thyroidectomy)
- Secondary to hypopituitarism, hypothalamic disorders.

Q. What are the thyroid functions in **secondary** hypothyroidism?

A. Low FT_3, FT_4 and TSH (Usually all thyroid hormones are low).

Q. How to **investigate** in such case?

A. Causes may be in the pituitary or hypothalamus. TRH stimulation test should be done. After giving TRH, if TSH is high, the cause is in the hypothalamus. If there is no or little rise of TSH, the cause is in the pituitary.

Q. If the patient has **ischemic heart disease** with hypothyroidism, how to treat?

A. As follows:

- Thyroxine should be given in low dose (25μg). Dose should be increased slowly up to the optimum dose
- β-blocker (propranolol) should be added
- Coronary dilator, calcium antagonist may be added
- Coronary angiography followed by angioplasty or coronary artery bypass surgery may be needed.

Q. How to treat an **elderly** patient with hypothyroidism?

A. Treatment is same. But one should take care whether the patient is suffering from any ischemic heart disease. Following thyroxine, it may precipitate angina and myocardial infarction. Treatment is same as above.

Q. Why **hypothyroidism** in **Graves'** disease?

A. Natural history of Graves' disease is hyperthyroidism, followed by euthyroidism and hypothyroidism (however, hypothyroidism may occur after radioiodine therapy or surgical treatment).

Q. What **bedside physical sign** will you see in myxedema?

A. Ankle jerk, which shows slow relaxation, also called "hung-up reflex" (other jerks may also show slow relaxation).

Q. How **slow relaxation** is best elicited in the ankle? **Why** slow relaxation?

A. It is best elicited in kneel down position on a chair or bedside. Slow relaxation is due to decreased rate of muscle contraction and relaxation.

Q. Why **nonpitting edema** in myxedema?

A. Due to deposition of mucopolysaccharide substances.

Q. What are the **types of anemia** in hypothyroidism?

A. Anemia may be:

- Usually normocytic normochromic
- Iron deficiency, if menorrhagia (in female)
- May be macrocytic due to associated pernicious anemia (due to deficiency of vitamin B_{12}).

Q. What are the **causes** of anemia in hypothyroidism?

A. Causes of anemia:

- Anemia of chronic disorder
- Iron deficiency
- Vitamin B_{12} deficiency

- Folate deficiency
- Other factors responsible—menorrhagia in female, anorexia.

Note

Macrocytosis in peripheral blood, but normoblastic bone marrow occurs in hypothyroidism

Q. What are the **cardiovascular** problems in myxedema?

A. As follows:

- Sinus bradycardia
- Pericardial effusion and pericarditis
- Congestive cardiac failure
- Atherosclerosis (because of hyperlipidemia)
- Ischemic heart disease
- Hypertension.

Q. What are the **neurological** features in hypothyroidism?

A. As follows:

1. Carpal tunnel syndrome (or tarsal tunnel syndrome).
2. Psychosis (myxedema madness).
3. Myxedema coma.
4. Cerebellar syndrome.
5. Deafness (Trotter's syndrome).
6. Others:
   - Epileptic fit (due to SIADH)
   - Peripheral neuropathy
   - Myotonia (Hoffman's syndrome)
   - Proximal myopathy
   - Pseudodementia
   - Drop attack.

Q. What is **Hoffman's syndrome**?

A. In a patient with myxedema, there may be myotonia with pain and swelling in the muscles after exercise, called Hoffman's syndrome.

Q. What is **Pendred's syndrome**?

A. It is an autosomal recessive disorder in which there is sensori-neural deafness with goiter. It is due to inborn error of thyroid hormone synthesis.

Q. What is **subclinical hypothyroidism** (borderline hypothyroidism or compensated euthyroidism)?

A. In this condition, T_3 and T_4 are in the lower limit of normal and TSH is slightly high. The patient may be clinically euthyroid. This may persist for many years, though overt hypothyroidism may occur. Conversion to overt hypothyroidism is more common in men or when thyroid peroxidase (TPO) antibody is present or TSH level is more than 10 mU/L.

Treatment—thyroxine therapy may be given if TSH is persistently raised above 10 mU/L or when there are symptoms or high titre of thyroid antibodies or lipid abnormalities. If only TSH is marginally high with vague symptoms, thyroxine may be given sometimes. However, in female TSH should be normalized during pregnancy to avoid any adverse effect in fetus.

If TSH is marginally raised, the test should be repeated after 3 to 6 months.

Q. What is the **difference** between primary and secondary hypothyroidism?

A. As follows:

- Primary hypothyroidism means cause in the thyroid gland. It is usually associated with myxedema.
- Secondary hypothyroidism means cause in the pituitary (or rarely hypothalamus). In such case, myxedema is rare. There are other features of hypopituitarism also.

Q. What is **myxedema coma?** What are the **mechanisms**? How to **treat**?

A. Myxedema coma is characterized by depressed level of consciousness or even coma. Convulsion may occur. It is rare, may occur in severe hypothyroidism, usually in elderly. CSF studies shows high pressure and protein is also high. There is 50% mortality.

Causes of myxedema coma:

- Syndrome of inappropriate ADH secretion (SIADH. Coma is due to hyponatremia)
- Hypoxemia
- Hypercapnia
- Hypothermia
- Hypoglycemia
- Other factors—cardiac failure, infection, use of sedative.

Treatment of myxedema coma: It is better to be treated in ICU. Before starting treatment, blood is taken for FT_3, FT_4, TSH and cortisol.

1. T_3 (rapidly acting) 20 µg, 8 hourly usually IV given (parenteral T_4 is not available, also slow to start action). If parenteral T_3 is not available, oral thyroxine through Ryle's tube should be given.
2. IV hydrocortisone—100 mg 8 hourly (especially if suspicion of hypopituitarism).
3. Other treatment:
   - Slow rewarming
   - High flow O_2 therapy
   - IV fluid and glucose
   - Antibiotic, if infection is suspected
   - Assisted ventilation may be necessary (as in any unconscious patient).

Q. What is **myxedema madness?**

A. It may occur in severe hypothyroidism in the elderly. There is dementia or psychosis or delusion. Sometimes, these features may occur shortly after starting thyroxine replacement. Depression is common in hypothyroidism.

Q. What is **sick euthyroid syndrome?**

A. In any severe acute nonthyroidal illness or after surgery, there may be abnormal thyroid function tests although the patient is euthyroid, it is called sick euthyroid syndrome. It may occur after myocardial infarction, pneumonia, cerebrovascular disease (CVD) and drugs (dopamine and steroid). Usually, there is normal TSH, normal or low T_4 and low T_3. Levels are usually mildly below normal and thought to be mediated by interleukins (IL-1 and IL-6). Test should be repeated after recovery of systemic illness.

Biochemical thyroid function should not be done in patient with acute nonthyroidal illness, unless there is good evidence of thyroid disease (such as goiter and exophthalmos).

Mechanisms of sick euthyroid syndrome:

- Reduced production or affinity of TBG to T_4 and T_3.
- Reduced peripheral conversion of T_4 to T_3, occasionally, more rT_3 (inactive reverse T_3).
- Reduced hypothalamic pituitary TSH production, hence low T_3 and T_4.

Q. How to investigate and treat **hypothyroidism in pregnancy**?

A. Hypothyroidism is difficult to diagnose in pregnancy, as normal pregnancy may be associated with many features of hypothyroidism such as cold skin, cold intolerance, weight gain, constipation. High degree of suspicion is essential.

- Most sensitive investigation is TSH, which is high. Also, FT_3 and FT_4 should be done (Total T_3 and T_4 may be high in normal pregnancy due to increase TBG).
- Treatment—thyroxine should be given (100 to 150 µg once daily). Requirement of thyroxine is relatively high (40 to 50%) in pregnancy, because of increased metabolism of thyroxine by the placenta and also increased serum TBG in pregnancy which binds thyroxine, resulting in less FT_3 and FT_4.
- Dose of thyroxine should be adjusted to maintain normal TSH (serum TSH and FT4 should be measured during each trimester).

Q. What is **Hashimoto's thyroiditis**?

A. It is an autoimmune thyroiditis characterized by destructive lymphoid infiltration of thyroid leading to atrophic change with regeneration and goiter formation. It is more common in middle aged woman.

- The goiter is usually diffuse, moderately enlarged and firm or rubbery. Sometimes, it may be soft to hard.
- Antithyroid antibody (very high, >1000 IU/L)—antimicrosomal (antiperoxidase) in 90% and antithyroglobulin antibodies (no rise of TSH-receptor antibody).
- About 25% patients are hypothyroid at presentation. In the remaining patients, serum T4 is normal and TSH is normal or raised. There is risk of developing overt hypothyroidism in future. Initially, the patient may present with features of toxicosis, called Hashi-toxicosis.
- In young patients (<20 years), ANF may be positive.
- Since this is an autoimmune disease, it may be associated with other autoimmune diseases like – Addison's disease, diabetes mellitus, premature ovarian failure, rheumatoid arthritis, Sjogren's syndrome, ulcerative colitis, autoimmune hemolytic anemia.
- Treatment – thyroxine (it reduces the size of goiter also).

Q. What is the **radio-iodine uptake** in Hashimoto's thyroiditis?

A. It shows the following:

- Initially—increased (toxic phase)
- After few days or weeks—normal uptake
- Later on—less uptake (hypothyroid phase).

Q. What are the **histological** findings in Hashimoto's thyroiditis?

A. As follows:

- Lymphocyte infiltration, also monocyte and plasma cell
- Hyperplasia and fibrosis
- Hurthle cell.

GRAVES' DISEASE (WITH THYROTOXICOSIS)

CHIEF COMPLAINTS

- Excessive sweating and heat intolerance for … months
- Weight loss for … months
- Palpitation for … months
- Insomnia, irritability and restlessness for … months
- Occasional loose motion for … months.

HISTORY

History of present illness: According to the statement of the patient, she was reasonably well … months back. Since then, she has been suffering from excessive sweating and heat intolerance. She prefers and feels comfortable in cold environment. She also noticed significant loss of weight inspite of her good appetite. She feels very hungry and takes more food, also experiences palpitation, even at rest which is more marked on exertion. She also complains of insomnia, irritability and restlessness for the last … months. The patient also complains of occasional loose stool, 3 to 4 times per day, which is not associated with mucus or blood and not related to intake of any food or milk. There is no history of fever, excessive thirst, polyuria or abdominal or chest pain.

History of past illness: Nothing significant

Family history: There is no such illness in her family. All the members of the family are in good health

Menstrual history: Her menstruation was regular. But for the last few months, she is amenorrhoic

Socioeconomic history: Mention according to the patient's statement

Drug and treatment history: There is no history of taking drugs that may cause these symptoms

GENERAL EXAMINATION

- The patient is emaciated and there is excessive sweating.
- The face appears anxious and frightened. There is bilateral exophthalmos with periorbital edema.
- Signs of thyrotoxicosis are present (tachycardia, warm sweaty palm, and fine tremor of outstretched hands).
- There is pretibial myxoedema (mention, if any).
- Pulse – 110/min, regular.
- BP – 160/85 mm Hg.

SYSTEMIC EXAMINATION

Thyroid Gland

- **Inspection**: The thyroid gland is diffusely enlarged, measuring 10 × 10 cm, right lobe is slightly larger than the left.
- **Palpation**: The gland is soft, nontender, mobile, surface is smooth, not fixed with underlying structure or overlying skin. Not associated with lymphadenopathy.
- **Percussion**: There is no retrosternal extension.
- **Auscultation**: There is bruit over the right lobe.

Eyes

- Exophthalmos—present in both eyes.
- Lid retraction and lid lag—present.
- Joffroy's sign—present.
- Mobius' sign and Stellwag's sign are absent.
- Movement of the eyeball—normal in all directions.

Note

Mention according to your findings

Cardiovascular System

- Pulse—110/min, regular, high volume.
- BP—160/85 mm Hg.
- Precordium—both first and second heart sounds are loud, no other abnormality detected.

Nervous System

- Higher psychic functions: She is irritable with a poor memory and concentration.
- Motor system:
  - Fine tremor of the outstretched hands
  - All the jerks—slightly brisk
  - Planter—flexor on both sides.
- Sensory system—intact.

SALIENT FEATURES

Mrs. …, 32 years old, housewife, normotensive, nondiabetic, hailing from …, presented with the complaints of excessive sweating and heat intolerance for … months. She prefers and feels comfortable in cold environment. She also noticed significant loss of weight inspite of her good appetite. She feels very hungry and takes more food, also experiences palpitation, even at rest which is more marked on exertion. She also complains of insomnia, irritability and restlessness for the last … months. The patient also complains of occasional loose stool, 3 to 4 times per day, which is not associated with mucus or blood and not related to intake of any food or milk. There is no history of fever, excessive thirst, polyuria or abdominal or chest pain. There is no such illness in her family. Her menstruation was regular. But for the last few months she is amenorrhoic. There is no history of taking drugs that may cause these symptoms. There is no family history of similar illness.

On Examination

General examination – mention as above.

Systemic examination – mention as above.

My diagnosis is thyrotoxicosis due to Graves' disease.

Q. Why it is Graves' disease?

A. Because, she has bilateral exophthalmos, diffuse goiter and dermopathy (pretibial myxedema).

Note. Remember the following -

If there is no exophthalmos, then tell the diagnosis as **thyrotoxicosis**. Then question may be asked, "What is the likely cause of thyrotoxicosis in this case?" Your answer will be "still it may be due to Graves' disease, as this is the commonest cause of thyrotoxicosis." Then mention other common causes of thyrotoxicosis.

Q. Why do you think this is a case of **thyrotoxicosis**?

A. Because:

- In the history, there is excessive sweating, weight loss inspite of good appetite, intolerance to heat, palpitation, and occasional loose motion.
- On examination, she is emaciated and signs of thyrotoxicosis, such as—tachycardia, warm sweaty palm and fine tremor of the out-stretched hands are present.

Note. Remember the following -

If a patient having loss of weight despite good appetite, think of thyrotoxicosis. (Other cause is diabetes mellitus). However, loss of appetite in thyrotoxicosis may occur in the elderly.

Q. What is your **differential diagnosis?**

A. Toxic nodular goiter, toxic multinodular goiter (sometimes, there may be small nodules which may not be palpable**.** Ultrasonogram of thyroid will show single or multiple nodular goiter).

Q. What are the **differences** between Graves' disease and toxic multinodular goiter?

A. As follows:

Features	Graves' disease	Toxic multinodular goiter
1. Age	20 to 40 years	Middle aged or elderly
2. Past history	Not specific	Nodular goiter for long time
3. Thyroid gland	Diffusely enlarged	Multinodular goiter
4. Cause	Autoimmune disease	Usually iodine deficiency
5. Ophthalmopathy	Common	Rare
6. Dermopathy	Common	Absent
7. Heart complications	Less common	More common
8. Thyroid acropachy	May occur	Absent
9. Hypothyroidism	May occur later	Usually does not occur

Q. What **investigations** do you suggest in thyrotoxicosis?

A. As follows:

1. To confirm thyrotoxicosis -

- FT_3, FT_4 and TSH (low TSH, high T_3 and T_4. But in T3 toxicosis, TSH is low and T_4 is normal, but T_3 is high).
- Radioiodine uptake test (RAIU) and thyroid scanning. RAIU shows rapid uptake and rapid turnover. There is high uptake in 2 or 4 and 24 hours, but rapid fall after 48 hours. Technetium scintigraphy is better than RAIU test because, it is quicker to perform and requires lower dose of radioactivity.

2. To find out causes:
   - Ultrasonography (USG) of the neck (to see single, multinodular and diffuse goiter).
   - Thyroid autoantibody (in Graves' disease) – TRAb (thyroid receptor antibody). TSH receptor stimulating antibody (TSI) is responsible for toxicosis.
   - Anti-peroxidase and anti-thyroglobulin antibody (very high in Hashimoto's thyroiditis, but slight to moderately high in Graves' disease).
3. Other tests:
   - Fine needle aspiration cytology, (FNAC, if goiter is present)
   - Electrocardiography (ECG)
   - Chest X-ray (to see retrosternal extension of goiter and cardiomegaly)
   - Blood sugar (may be high as secondary DM may occur)
   - Serum cholesterol (low in thyrotoxicosis)
   - For ophthalmopathy – ocular ultrasonography, CT scan of the orbit.

Q. What are the **findings** of radio iodine uptake test in thyrotoxicosis?

A. It shows—rapid uptake and rapid turnover (After 2 or 4 and 24 hours, uptake is high. After 48 hours, uptake falls).

Q. What are the causes of **thyrotoxicosis with low radioiodine uptake?**

A. As follows:
- Subacute thyroiditis (De Quervain's thyroiditis).
- Postpartum thyroiditis.
- Factitious thyrotoxicosis.
- Iodine induced (if the patient is on iodine or amiodarone, which contains iodine).
- Ectopic thyroid tissue producing thyrotoxicosis (struma ovarii, choriocarcinoma and hydatidiform mole).

QUESTIONS AND ANSWERS RELATED TO GRAVES' DISEASE

Q. What is **Graves' disease?**

A. It is an autoimmune thyroid disease due to stimulating antibody against TSH receptors (thyroid stimulating immunoglubulin- TSI), characterized by **triad** of:
- Exophthalmos
- Diffuse goiter
- Dermopathy (pretibial myxedema).

Q. What is the **cause** of Graves' disease?

A. Autoimmune disease due to IgG antibody against TSH receptor, producing excess thyroid hormones. TRAb antibody acts similar to TSH. Common in female, M:F = 1:5. TRAb is of two types: (1) TSI, 80% to 95%, causing thyrotoxicosis and (2) TSH receptor blocking antibody, causing hypothyroidism.

Q. What is the significance of **thyroid bruit**?

A. It is pathognomonic of Graves' disease, and it rarely occurs in other thyroid diseases. It indicates increased vascularity, probably due to autoimmune mechanism.

Q. What is the **natural history** of Graves' disease?

A. It may be hyperthyroid, euthyroid followed by hypothyroidism.

Q. What is **euthyroid** Graves' disease?

A. The patient is clinically and biochemically euthyroid, but there is ophthalmopathy (also there is diffuse goiter, dermopathy). Thyroid releasing hormone (TRH) stimulation test show flat response curve.

Q. What is **hypothyroid Graves' disease**?

A. In this condition, the patient has features of Graves' disease (see above) with the following features of hypothyroidism:

- Coarse puffy face, periorbital puffiness (baggy eye lids)
- Dry, cold and scaly skin
- Nonpitting edema, slow relaxation of the ankle jerk
- Coarse and croaky voice.

Q. What is the **mechanism** of thyroid ophthalmopathy? What are the **changes** and how to **treat?**

A. It is immunologically mediated. Within the orbit, there is cytokine-mediated proliferation of fibroblast, which secretes hydrophilic glycosaminoglycans.

The following changes occur in ophthalmopathy:

- Excessive interstitial fluid and infiltration of chronic inflammatory cells in the orbit (lymphocytes, plasma cells and mast cells)
- Swelling and edema of extraocular muscles
- Increased retrobulbar pressure and eyeball is pushed forward (proptosis). In severe cases, optic nerve compression may occur.

Clinical features: Increased lacrimation, gritty sensation in the eye, pain due to conjunctivitis or corneal ulcer, reduced visual acuity and diplopia. It increases with poor control of thyroid function and also following radioiodine therapy. Ophthalmopathy is common in cigarette smoker. However, cigarette smoking is weakly associated with Graves' disease.

Treatment:

- Reassurance and general treatment of the eye. Methylcellulose eyedrops (relieves grittiness). To prevent exposure keratitis, use tinted glass and lateral tarsorrhaphy (if corneal ulcer).
- If visual field defect, loss of visual acuity and papilledema or progressive exophthalmos, steroid in high dose (prednisolone 60 to 120 mg/day) may be helpful.
- Pulse methylprednisolone and cytotoxic drug (cyclophosphamide) may be helpful.
- In severe cases—irradiation of the orbit.
- If no response in 7 to 10 days or loss of visual acuity, orbital decompression may be necessary.
- For diplopia—correction of eye muscle by surgery (but should be delayed for 6 months, until degree of diplopia is stable).

Note. Remember, ophthalmopathy in Graves' disease -

- Eye problems occur in 5% to 10% of the cases.
- Ophthalmopathy occurs in 50% in the first presentation, may develop after treatment of hyperthyroidism and precedes many years before hyperthyroidism.
- Not related to toxicosis. It may be present in euthyroid or hypothyroid.
- If hypothyroidism develops, exophthalmos may be aggravated, especially if treated with radioiodine therapy.
- Lid retraction resolves when the patient is euthyroid, but exophthalmos resolves slowly and may take up to 2 to 3 years.

Eponyms of eye signs in thyroid disease:

- Lid lag—von Graefe's sign
- Absence of wrinkling of forehead on upward gaze—Joffroy's sign
- Impaired convergence of eye—Möebius' sign
- Infrequent blinking—Stellwag's sign

- Paralysis of extraocular muscles—Jendrassik sign.
- Weakness of at least one extraocular muscle—Ballet sign.

Q. What is **malignant exophthalmos?**

A. It is the severe, progressive exophthalmos which may lead to blindness due to optic nerve compression. Treated with high dose of prednisolone up to 120 mg/day. Decompression may be needed, sometimes orbital irradiation may be given.

Q. What is **pretibial myxedema** (dermopathy)?

A. In this condition, there is firm, nodular, thickened or plaque-like lesion, pink or brown, giving a peau d'orange appearance. It is due to the deposition of mucopolysaccharide in the dermis. Usually, present in the shin of legs up to the dorsum of foot (but may occur in any part of the body, especially at pressure point). It may be pruritic and hyperpigmented. It is present only in Graves' disease in 10% cases, almost always associated with ophthalmopathy and is not a manifestation of hypothyroidism (pretibial myxedema is a misnomer). Occasionally, pretibial myxedema develops after treatment of hyperthyroidism, especially with radioiodine therapy.

Treatment is rarely necessary. Local injection of triamcinolone or ointment betamethasone may be helpful.

Q. Is there any **evidence of cancer** in Graves' disease?

A. Unusual, but highly suspicious if there is associated cold nodule.

Q. How to **treat** Graves' disease?

A. Graves' disease is an autoimmune disease which may present with hyper, hypo or euthyroid state.

- If there is thyrotoxicosis or hypothyroidism treat accordingly
- In euthyroid cases, treatment is only symptomatic and supportive.

QUESTIONS AND ANSWERS RELATED TO THYROTOXICOSIS

Q. What are the **causes** of thyrotoxicosis?

A. As follows:

1. Graves' disease—commonest cause (76%).
2. Toxic multinodular goiter (14%).
3. Toxic nodular goiter (5%, toxic adenoma or hot nodule called Plummer's disease).
4. Thyroiditis (subacute thyroiditis, also called De Quervain's thyroiditis, and postpartum thyroiditis. All are transient).
5. Hashimoto's thyroiditis, also called Hashitoxicosis (ultimately hypothyroidism develops).
6. Factitious thyrotoxicosis (self-intake of thyroxine).
7. Iodine induced (Jod-Basedow's phenomenon) and drug (amiodarone).
8. Others (rare):
   - Carcinoma of thyroid (follicular)
   - Struma ovarii (secretes thyroid hormone)
   - Hydatidiform mole and choriocarcinoma (both secrete thyroid-stimulating hormone, TSH).

Q. What is **factitious thyrotoxicosis?**

A. Features of thyrotoxicosis that occur following deliberate intake of thyroxine to reduce weight, usually in emotionally disturbed person. Clues for diagnosis are high thyroid hormones and low radioiodine uptake. Thyroglobulin level is zero or low. There is high ratio of T_4:T_3 = 70:1 (in conventional thyrotoxicosis, the ratio is 30:1). Combination of negligible radioiodine uptake, high T_4:T_3 ratio and low thyroglobulin is diagnostic.

Note. Remember the following points:

- In elderly patient, there may not be obvious features of thyrotoxicosis. Sometimes, the patient may present only with atrial fibrillation, tachycardia or heart failure, which masks the features of thyrotoxicosis.
- Children may present with excess growth, behavior problem like hyper-reactivity and increase in weight rather than loss.
- Apathetic thyrotoxicosis may be present in elderly patient. There are features of thyrotoxicosis associated with features of hypothyroidism also. High degree of suspicion is essential for the diagnosis of such case.

Q. What is **thyrotoxic periodic paralysis** (TPP)?

A. If a thyrotoxic patient develops sudden or periodic weakness, it is called TPP. It is due to hypokalemia (caused by entry of potassium into the cell), common in Asians. It may occur following excess intake of carbohydrate or glucose or after heavy exercise and may persists for 7 to 72 hours. Treatment of thyrotoxicosis improves the condition.

Q. How to **treat** thyrotoxicosis?

A. Three modes of treatment: drugs (carbimazole and propylthiouracil), radioiodine therapy and surgery.

1. Drugs:

- Carbimazole or propylthiouracil: These drugs reduce the synthesis of thyroid hormones by inhibiting the iodination of tyrosine.
  - Carbimazole 45 to 60 mg daily. When the patient is euthyroid, reduce the dose, then 5 to 20 mg daily for 18 to 24 months. Periodic complete blood count (CBC) is necessary, as there may be agranulocytosis. Also, FT_4 and TSH should be measured.
  - Propylthiouracil 400 to 600 mg daily. Dose is reduced when the patient becomes euthyroid.
- β-blocker: Propranolol (up to 160 mg/day). It reduces sympathetic symptoms (such as tremor, tachycardia and sweating).

Indications of drug:

- Usually given in first episode in patient < 40 years of age.
- Small goiter.
- Mild features of thyrotoxicosis.

Disadvantages of drugs:

- Relapse in 50% of the cases within 2 years of stopping the drug (surgery or radioiodine or long-term drug therapy may be needed in such case).
- Complication such as hypersensitive skin rash and agranulocytosis.
- Compliance may be poor.
- Costly.

Note. Remember the following -

Advise the patient with carbimazole therapy—if sore throat or fever develops, which may be due to agranulocytosis, stop the drug and inform the doctor.

2. Radioiodine therapy: It acts by destroying the functioning thyroid cells and by inhibiting their ability to replicate. About 5 to 10 mCi is given orally, depending on the size of goiter. It is effective

in 75% cases in 4 to 12 weeks. In this period, propranolol is given. In severe cases, carbimazole may be given, which should be started 48 hours after radioiodine therapy. If the drug is started before 48 hours, it reduces the efficacy of radioiodine.

Indications of radioiodine therapy:

- Usually, above 40 years of age (however, some advocate to use in young)
- Recurrence after surgery or drugs, irrespective of age
- Toxic multinodular goiter or toxic adenoma or hot nodule
- In early age, with major serious other illness
- Some cases of carcinoma thyroid (follicular, papillary after surgery)
- Ablative therapy with severe atrial fibrillation, also in heart failure
- Psychosis
- Poor drug compliance
- Hypersensitivity to the drug.

Contraindications of radioiodine therapy:

- Pregnancy or planned pregnancy within 6 months of treatment.
- During lactation.
- Active or malignant Graves' ophthalmopathy**.**

Disadvantages of radioiodine therapy:

- Hypothyroidism: It occurs in 40% in first year and 80% in 15 years.
- Early discomfort and exaggeration of hyperthyroidism may occur (due to radiation thyroiditis). Hence, the patient should be rendered euthyroid using drug, which should be stopped 2 to 5 days before radioiodine therapy.
- Exacerbation of ophthalmopathy.

Note. Remember the following -

In severe thyrotoxicosis, initially carbimazole is given for 4 to 8 weeks. Then radioiodine therapy is given. Carbimazole is stopped 48 hours before radioiodine therapy. If no response after 12 to 24 weeks, a second dose of radioiodine is given.

3. Surgery (subtotal thyroidectomy): The patient should be made euthyroid by antithyroid drug before operation. Two weeks before operation, potassium iodide should be added 60 mg 8 hourly. It inhibits thyroid hormone release, reduces the size and vascularity of gland, making surgery technically easier.

Indications of surgery:

- Large goiter or multinodular goiter
- Relapse or no response to drug
- Drug hypersensitivity
- Noncompliance with drug
- Suspicion of malignancy
- Pressure effect
- Cosmetic purpose.

Complications of surgery:

- Hypothyroidism in 25%

- Transient hypoclcemia (10%)
- Permanent hypoparathyroidism (1%)
- Recurrent laryngeal nerve palsy, causing hoarseness of voice due to vocal cord palsy (1%).

Note. Remember the following -

In toxic nodular or multinodular goiter, treatment of choice is radioiodine therapy or surgery. Drug treatment is not helpful.

Q. How to **treat** thyrotoxicosis **with atrial fibrillation**?

A. Atrial fibrillation occurs in 10% cases, common in the elderly > 60 years, more in toxic multinodular goiter, and may occur in subclinical hyperthyroidism. It is treated by:

- β-blocker: Propranolol (digoxin has little role). Verapamil and amiodarone may be used, if β-blocker is contraindicated.
- Antithyroid drug, followed by radioiodine therapy.
- Anticoagulant: Aspirin in elderly and warfarin in younger.
- 50% AF reverts spontaneously to sinus rhythm. If persistent AF is present, cardioversion may be done, provided FT_4 and TSH are normal.

Q. How to **treat** thyrotoxicosis in **pregnancy**?

A. The patient with thyrotoxicosis is unlikely to get pregnant as anovulatory cycles are common. Autoimmune thyroid disease is also less common as maternal immune response is suppressed in pregnancy. Diagnosis may be difficult, because of the overlap symptoms of normal pregnancy (e.g. palpitation) and also misleading thyroid function test, although TSH is usually reliable.

Because of high thyroxine binding globulin (TBG), total T_4 and T_3 are high, and TSH is low. Hence, high FT_4 and FT_3, and low TSH level is suggestive of thyrotoxicosis. In pregnancy, thyrotoxicosis is usually due to Graves' disease. TRAb (TSI) can cross placenta and develop thyrotoxicosis in fetus also.

Treatment of thyrotoxicosis in pregnancy:

- Propylthiouracil is preferred (carbimazole can cross placenta, causing fetal goiter and scalp skin defect in child called aplasia cutis). Propylthiouracil is given in lowest dose, less than 150 mg daily to prevent fetal hypothyroidism and goiter. TRAb is measured in last trimester. If it is not high, the drug can be stopped 4 weeks before delivery (to prevent neonatal hypothyroidism).
- If needed, propylthiouracil can be given after delivery and breastfeeding should be continued, as little drug is excreted in breast milk.
- If surgery is necessary, it should be done in middle trimester.

Note. Remember the following -

Radioiodine therapy is absolutely contraindicated in pregnancy.

Q. What is **thyrotoxic crisis**? How to **treat**?

A. Thyrotoxic crisis is characterized by life threatening increase of signs and symptoms of thyrotoxicosis (also called thyroid storm).

Features of thyrotoxic crisis are:

- High fever
- Restlessness, agitation and irritability

- Nausea, vomiting, diarrhea and abdominal pain
- Tachycardia, AF and in elderly, cardiac failure
- Confusion, delirium and coma.

Precipitating factors for thyroid crisis:

- Infection
- Stress
- Surgery in unprepared patient
- Following radioiodine therapy (due to radiation thyroiditis).

Diagnosis—mostly clinical and high degree of suspicion is vital. FT_3, FT_4 and TSH should be done immediately.

Treatment (blood sample is taken for T_3, T_4 and TSH):

- The patient should be treated in intensive care unit (ICU).
- Propranolol 80 mg 6 hourly (or 1 to 5 mg IV 6 hourly).
- IV fluid (normal saline and glucose).
- Carbimazole 40 to 60 mg daily. Or propylthiouracil 150 mg 6 hourly (if needed, through Ryle's tube). Carbimazole can be given per rectally also.
- Other therapy—sodium ipodate, a radiographical contrast media, 500 mg daily is rapidly effective. Or potassium iodide or Lugol's iodine may be given. Dexamethasone 2 mg 6 hourly and amiodarone are also effective.
- Broad spectrum antibiotic.
- General measures—control of temperature and O_2 therapy.
- After 10 to 14 days, the patient can usually be maintained on carbimazole alone.

Mortality rate in thyrotoxic crisis is 10%.

CUSHING'S SYNDROME

CHIEF COMPLAINTS

- Excessive weight gain for … months
- Weakness for … months
- Backache and generalized bodyache for … months
- Bleeding spots on the skin for … days.

HISTORY

History of present illness: According to the statement of the patient, she was reasonably well … months back. Since then, she is gaining weight which is progressively increasing inspite of normal food intake. She also feels extremely weak and lethargic. The patient also complains of backache and generalized bodyache for the last … months. The pain is more marked with activity and the patient feels comfortable by taking rest. Sometimes, she feels difficulty in standing from sitting position. For the last … months, she noticed multiple bleeding spots on the skin, involving mostly the forearms and legs. There is no history of headache, visual problem, cough or chest pain. Her bowel and bladder habits are normal. There is no history of intolerance to cold, or increased sleepiness.

History of past illness: Nothing significant.

Menstrual history: She gives history of oligomenorrhea (or amenorrhea) for … months, previously it was regular.

Family history: Nothing significant.

Socioeconomic history: Nothing significant.

Drug and treatment history: There is no history of intake of steroid and alcohol.

GENERAL EXAMINATION

- The patient is obese. There is more truncal obesity with relatively lean and thin limbs (lemon on a match stick appearance)
- Face is moonlike, puffy and plethoric with acne, hirsutism and frontal baldness
- There is buffalo hump at the root of the neck and increased fat above both the supraclavicular fossa
- There are multiple pink striae on abdomen, back and axilla
- Skin is thin, with multiple purpura and bruise
- Pulse—90/min, regular
- BP—155/90 mm Hg
- Temperature—98.6°F
- Respiration—16/min.

SYSTEMIC EXAMINATION

Abdomen

- The abdomen looks distended and flanks are full
- There are multiple pink striae of variable size and shape
- No organomegaly
- Ascites—absent (as evidenced by absent fluid thrill and shifting dullness)

Cardiovascular System

- Pulse—90/min
- BP—155/90 mm Hg
- Precordium—normal.

Nervous System

- Higher psychic functions—normal
- Cranial nerves—intact
- Motor system—proximal muscular weakness of both upper and lower limbs. Reflexes are normal
- Sensory system– normal.

Musculoskeletal System

- Proximal myopathy is present more marked in the lower limb than upper limb
- There is slight kyphosis
- Spine is tender at lumbar region (due to osteoporosis).

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mrs. …, 40 years old, housewife, normotensive, nondiabetic, hailing from …, presented with weight gain for … months, which is progressively increasing inspite of normal food intake. She also feels extremely weak and lethargic. The patient also complains of backache and generalized bodyache for the last … months. The pain is more marked with activity and the patient feels comfortable by taking rest. Sometimes, she feels difficulty in standing from sitting position. For the last … months, she noticed multiple bleeding spots on the skin, involving mostly the forearms and legs. There is no history of headache, visual problem, cough or chest pain. Her bowel and bladder habits are normal. There is no history of intolerance to cold, or increased sleepiness. She gives history of oligomenorrhea (or amenorrhea) for … months, previously it was regular. There is no history of intake of steroid and alcohol.

On Examination—

General examination – mention as above.

Systemic examination – mention as above.

My diagnosis is cushing's syndrome.

Q. What are your **differential diagnoses?**

A. As follows:

- Simple obesity
- Hypothyroidism
- Metabolic syndrome
- PCOS (in early age).

Q. How to **investigate** Cushing's syndrome?

A. Initial tests are done to confirm the diagnosis and further tests are done to find out the cause.

1. Tests to confirm Cushing's syndrome:
   - First line screening test:

- 24 hours urinary free cortisol measurement
- Overnight dexamethasone suppression test—1 mg dexamethasone is given orally at 11 p.m. Blood sample is taken at 9 a.m. in the next morning to measure serum cortisol. Normally, almost total suppression of cortisol (< 100 nmol/L). Failure of suppression indicates Cushing's syndrome due to any cause (This test is simple, can be done as an outpatient screening test, but gives some false positive results).

♦ Second line screening test (if above are abnormal)
- Serum cortisol level (8 a.m. and 12 midnight)—shows loss of circadian rhythm. Normally, serum cortisol is high in morning and low in midnight (called circadian rhythm).
- Low dose dexamethasone suppression test—0.5 mg 6 hourly for 2 days. Measure serum cortisol at 9 a.m. on days 0 and 2. Failure of suppression of cortisol (< 60 nmol/L on second sample) indicates Cushing's syndrome due to any cause. Or, 24 hour urine free cortisol < 100 nmol/day also excludes Cushing syndrome.

2. Tests to find out the cause (to localize the site of lesion):

♦ Serum ACTH:
- If ACTH is low or undetectable, adrenal cause is likely. Then USG, CT or MRI of abdomen is done to find adrenal tumor. If no mass is seen, then adrenal vein sampling or adrenal scintigraphy should be done.
- If ACTH is high—likely cause is pituitary lesion (Cushing's disease) or ectopic ACTH syndrome. Then, high dose dexamethasone suppression test or corticotrophin releasing hormone test is done to differentiate between these two.
  a. High dose dexamethasone suppression test—2 mg 6 hourly for 2 days. Plasma cortisol is measured at 9 am on days 0 and 2. Plasma cortisol on day 2 less than 50% of that in day 0 suggests Cushing's disease (in 90% cases). Failure of suppression occurs in ectopic ACTH and adrenal tumor. Urine cortisol < 50% of basal suggests Cushing's disease and > 50% of basal suggests ectopic ACTH syndrome.
  b. Corticotropin releasing hormone (CRH) test—100 µg bovine CRH IV is given. Measure serum ACTH and cortisol for 2 hours. It increases in Cushing's disease, but no response in ectopic ACTH (Peak plasma cortisol >120% and/or ACTH > 150% of basal values suggest pituitary disease).

♦ If Cushing's disease is present—CT or MRI of skull. MRI will show pituitary microadenoma in 70% cases. If no mass is seen, selective catheterisation of inferior petrosal sinus to measure ACTH for pituitary lesion.

♦ If ectopic ACTH syndrome is the cause—chest X-ray, CT scan of chest (to see carcinoma of bronchus or bronchial carcinoid).

3. Other tests (to see the effect):

♦ Electrolytes (hypokalemia).

♦ Blood sugar

♦ Bone mass density to see osteoporosis.

Note. Remember the following points:

➡ Plasma cortisol levels are highly variable. So, random measurement of daytime plasma cortisol level is of no value.

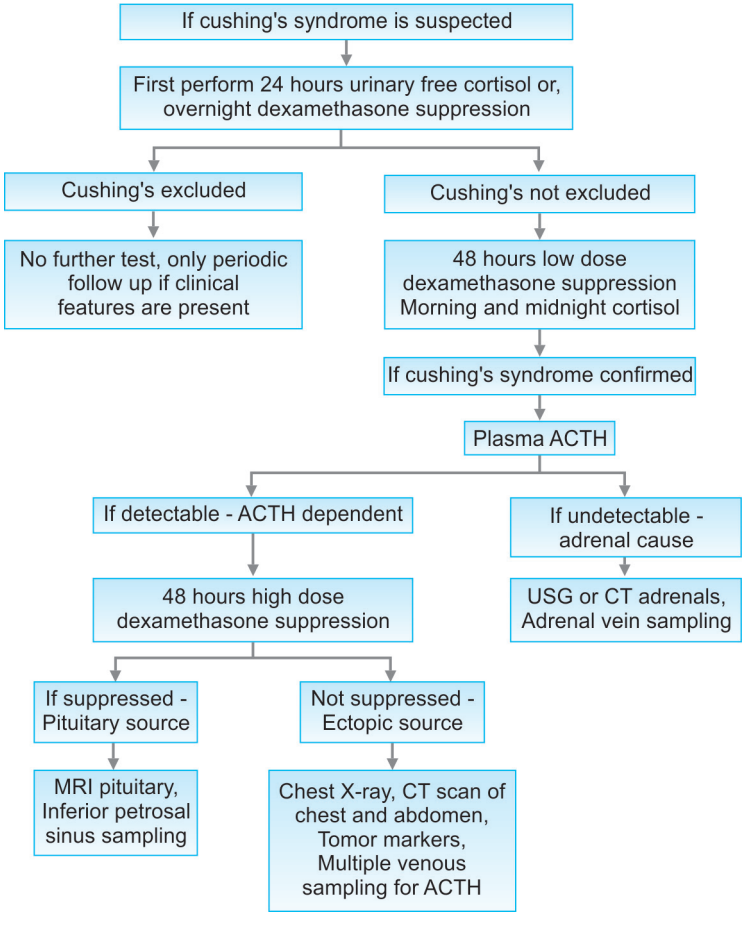
➡ In pituitary tumor, there is high ACTH and high cortisol.

➡ In ectopic ACTH syndrome, there is high ACTH and high cortisol.

➡ In adrenal tumor, there is low or undetectable ACTH and high cortisol.

➡ Cushing's disease and cortisol secreting adrenal tumor are 4 times common in women than men. But ectopic ACTH syndrome is more in men.

Systematic investigation in cushing syndrome


If cushing's syndrome is suspected
First perform 24 hours urinary free cortisol or, overnight dexamethasone suppression
Cushing's excluded
Cushing's not excluded
No further test, only periodic follow up if clinical features are present
48 hours low dose dexamethasone suppression Morning and midnight cortisol
If cushing's syndrome confirmed
Plasma ACTH
If detectable - ACTH dependent
If undetectable - adrenal cause
48 hours high dose dexamethasone suppression
USG or CT adrenals, Adrenal vein sampling
If suppressed - Pituitary source
Not suppressed - Ectopic source
MRI pituitary, Inferior petrosal sinus sampling
Chest X-ray, CT scan of chest and abdomen, Tomor markers, Multiple venous sampling for ACTH

Q. Why dexamethasone is used in suppression test? **Why** not other steroids like prednisolone?

A. Because, dexamethasone does not cross react in radioimmunoassay for cortisol. But other steroids can cross react.

Q. Why the patient may complain of **backache**?

A. Osteoporosis (may cause vertebral collapse and kyphosis).

Q. How to **treat** Cushing's syndrome?

A. It depends on the cause.

1. Cushing's disease:
   - Transphenoidal removal of microadenoma
   - If surgery is not possible or unsuccessful, bilateral adrenalectomy should be done. Later, the patient may develop Nelson's syndrome (see below)
   - If surgery is not possible, sometimes only pituitary irradiation may be given. External irradiation is given. It is slowly effective in 50% to 60% cases, response in children is better than adults, 80% may be cured

- To reduce ACTH production—bromocriptine or cyproheptadine is rarely effective
- Drugs such as metyrapone and ketoconazole may be given.

2. Adrenal tumor:
   - In adrenal adenoma or carcinoma, surgical resection is done (adrenalectomy)
   - In carcinoma, there is chance of recurrence. Then, radiotherapy or chemotherapy or adrenolytic drugs like mitotane may be given
   - Other drugs—metyrapone or ketoconazole may be used (which inhibits biosynthesis of cortisol).
3. Ectopic ACTH:
   - If possible, the primary lesion should be surgically removed (like bronchial carcinoma or carcinoid). Other treatment of the primary cause like radiotherapy or chemotherapy should be considered
   - If surgery is not possible, medical therapy as above or bilateral adrenalectomy may be considered.

RELATED QUESTIONS AND ANSWERS

Q. What is **Cushing's syndrome**? What are the common **features**?

A. It is defined as symptoms and sign due to chronic glucocorticoid excess whatever its cause. High glucocorticoid leads to constellation of symptoms and signs, commonly:

- Weight gain but weakness
- Proximal muscular weakness (characterized by difficulty in combing, raising the hands above the head, standing from squatting)
- Hirsutism in female
- Amenorrhea or oligomenorrhea
- Loss of libido
- Backache, pathological fracture (due to osteoporosis), collapse of the vertebra with reduction of height
- Easy bruising, purple abdominal striae
- Hypertension, diabetes mellitus (30%) or IGT
- Frequent infection, especially fungal infection, slow wound healing
- Mood disturbance like depression, insomnia, irritability, lethargy
- On examination—moon face, buffalo hump, truncal obesity, hirsutism, acne on face, pink striae, growth retardation in children.

Q. What are the causes of **moon face** or puffy face?

A. As follows:

- Cushing's syndrome (plethoric moon face, with hirsutism, acne)
- Myxedema (puffy with baggy eyelids, fall of lateral eyebrows, malar flush)
- Nephrotic syndrome and acute glomerulonephritis (puffy with periorbital oedema)
- Superior vena caval obstruction (engorged and non pulsatile veins, plethoric face with subconjunctival effusion)
- Angioedema (localized, swollen lip or face)
- Chronic alcoholism (plethoric, puffy face)
- Simple obesity
- Surgical emphysema (history of trauma, also swelling is extended upto the neck and chest. There are multiple crepitations on palpation).

Q. What are the causes of **periorbital edema?**

A. As follows:

- Nephrotic syndrome
- Acute glomerulonephritis
- Myxedema
- Angioedema
- Dermatomyositis
- Orbital cellulitis
- Malignant exophthalmos.

Q. What is the **commonest cause** of Cushing's syndrome?

A. Iatrogenic steroid therapy or ACTH (for long time). Non-iatrogenic Cushing's syndrome is very rare.

Q. What are the **causes** of Cushing's syndrome?

A. Commonest cause is steroid therapy. Other causes:

1. ACTH dependent
   - Pituitary microadenoma < 10 mm, called Cushing's disease (in 80% cases). Common in women
   - Ectopic ACTH syndrome (due to oat cell carcinoma of bronchus, bronchial adenoma, bronchial carcinoid and carcinoma of pancreas)
   - ACTH therapy.
2. Non-ACTH dependent
   - Prolong steroid therapy—the commonest cause (even topical or inhaled steroid for long time in susceptible cases may be responsible)
   - Adrenal adenoma and adrenal carcinoma (common in women).
3. Others—Pseudo-Cushing's syndrome (due to alcohol, depression and obesity).

According to source, causes may be:

1. Exogenous: Prolong steroid therapy (ACTH independent).
2. Endogenous:
   - Pituitary cause (85%, ACTH dependent)
   - Adrenal tumor (ACTH independent)
   - Ectopic production of ACTH (ACTH dependent).

Q. What is the **difference** between Cushing's disease and Cushing's syndrome?

A. As follows:

- Cushing's disease—there is increased production of ACTH from pituitary that stimulates adrenals
- Cushing's syndrome is caused by excess glucocorticoid due to any cause.

Q. What is **Pseudo-Cushing's** syndrome?

A. Cortisol excess due to other illness without involvement of the pituitary adrenal axis is called Pseudo-Cushing's syndrome. There is increased urinary excretion of steroid, absent diurnal variation of cortisol and failure of suppression by dexamethasone.

- It may occur in chronic alcoholism, severe depression and in simple obesity. All the features of Cushing's syndrome revert to normal after removal of the cause (features in favor of Cushing's syndrome are bruise, myopathy and hypertension, all of which are usually absent in Pseudo-Cushing's syndrome).
- To differentiate from Cushing's syndrome—insulin induced hypoglycemia is helpful. In Cushing's syndrome, almost no response. But in Pseudo-Cushing's syndrome, there is excess cortisol secretion.

Note. Remember the following -

Remember, if there is history of alcohol intake, advice the patient to stop taking alcohol. Repeat the cortisol or dexamethasone suppression test. It may be normal. Then further test is not recommended.

Q. What are the indications of **long-term steroid therapy**?

A. Steroid is used for long time in:

- Replacement therapy in Addison's disease and also in hypopituitarism (lifelong)
- Systemic lupus erythematosus (SLE).
- Idiopathic fibrosing alveolitis
- Dermatomyositis
- Pemphigus vulgaris
- Chronic active hepatitis (CAH)
- Giant cell arteritis.

Q. Tell one **absolute indication** of steroid therapy?

A. Pemphigus vulgaris (also, Addison's disease, bilateral adrenalectomy, giant cell arteritis, severe SLE, etc.)

Q. What are the **striae** in Cushing's syndrome?

A. Striae are pink or purple coloured lesions in the skin of abdomen and other parts of body.

Q. What is **striae**? What are the **causes**?

A. These are wrinkled, linear, white or pink-colored marks over the skin. Striae is due to stretching of skin, causing rupture of elastic fibres. Causes of striae are:

- Striae gravidarum (white or pink, narrow lines, in abdominal wall due to pregnancy and usually below the umbilicus).
- Obesity (whitish narrow lines, usually longitudinal, < 2 mm).
- Cushing's syndrome (wide lines, pink or purple or red, mostly horizontal or oblique. Pink or red color is due to increased vascularity).

Q. How to **differentiate clinically** different types of Cushing's syndrome?

A. By history, physical examination and investigation:

1. In Cushing's syndrome due to adrenal cause:
   - In adrenal adenoma—clinical features of glucocorticoid excess are present but androgenic effect like hirsutism and virilisation are absent and no pigmentation.
   - In adrenal carcinoma—clinical features of glucocorticoid excess are present and androgenic effect like hirsutism and virilisation are rapidly progressive.
2. In ectopic ACTH syndrome—usually there is short history, excess pigmentation due to high ACTH level, weight loss (rather than obesity) and severe hypokalemic alkalosis. Hypertension and edema are more common. Classical features of Cushing's syndrome are usually absent. Features of the primary lesion are present.
3. In Cushing's disease—classic features of Cushing's syndrome are present. If there is pituitary macroadenoma, visual disturbance and features of hypopituitarism may be present. There may be features of raised intracranial pressure like headache.
4. Marked hypoklemia suggests ectopic ACTH syndrome.
5. History of alcoholism and depression or simple obesity suggests pseudo-Cushing's syndrome.

Q. What are the **causes of death** in Cushing's syndrome?

A. Death may be due to:

- Hypertension and its complications
- Myocardial infarction
- Heart failure
- Infections.

Q. What is **Nelson's syndrome**?

A. After bilateral adrenalectomy in Cushing's disease, there may be increased pigmentation due to excess ACTH, it is called Nelson's syndrome. It is due to enlarging pituitary tumor in the absence of negative feedback suppression, due to absence of cortisol after adrenalectomy.

It occurs in around 20% cases. The tumor is locally invasive. It can be prevented by pituitary radiotherapy soon after adrenalectomy.

Treatment: Surgical removal of the tumor. Occasionally, radiotherapy (if not given previously).

ADDISON'S DISEASE

CHIEF COMPLAINTS

- Weakness and weight loss for … months.
- Loss of appetite, nausea, dizziness and vertigo for … months.
- Pigmentation in different parts of the body for … months.

HISTORY

History of present illness: According to the statement of the patient, she was reasonably well … months back. Since then, she has been suffering from severe weakness with gradual loss of about 10 kg of bodyweight. The patient also complains of loss of appetite, nausea, dizziness and vertigo for the last … months. Her dizziness and vertigo are more marked when sitting from lying position and on standing. There is no history of fever, cough, bowel or bladder abnormality, excessive sweating, palpitation or heat intolerance. For the last … months, she also noticed some pigmentation involving different parts of the body. There is no history of injury or recent scar.

History of past illness: She gives no history of tuberculosis, abdominal trauma or surgery.

Family history: Nothing significant. There is no history of such illness in the family.

Socioeconomic history: Mention according to the statement of the patient.

Menstrual history: Amenorrhea for the last 4 months, but it was regular previously.

Drug and treatment history: There is no history of intake of steroid or any other drugs.

GENERAL EXAMINATION

- The patient is ill looking and emaciated
- There is generalized pigmentation, more marked on the face, neck, mucous membrane of the mouth, palmar crease, knuckles, knees and elbows
- One vitiligo is present over the right thigh
- Sparse (or less) axillary and pubic hair
- No anemia, jaundice, cyanosis, clubbing, koilonychia, leukonychia, edema
- Pulse—96/min
- BP—lying 100/60 mm Hg and standing 70/40 mm Hg.

Examination of other systems reveals normal findings.

SALIENT FEATURES

Mrs. …, 35 years old, housewife, hailing from …, presented with the complaints of severe weakness with gradual loss of about 10 kg of bodyweight for … months. She also complains of loss of appetite, nausea, dizziness and vertigo for the last … months. Her dizziness and vertigo are more marked when sitting from lying position and on standing. There is no history of fever, cough, bowel or bladder abnormality, excessive sweating, palpitation, heat or cold intolerance. For the last … months, she also noticed some pigmentation involving different parts of the body. There is no history of injury or recent scar. She never suffered from tuberculosis in the past. She has been amenorrheic for the last 4 months. She did not take steroids or any other drugs. There is no family history of similar illness.

On Examination

General examination – mention as above.

Systemic examination – mention as above.

My diagnosis is Addison's disease.

Q. Why **your diagnosis** is Addison's disease?

A. There is weakness and weight loss, hypotension with postural drop and pigmentation. All these are suggestive of Addison's disease.

Q. What are your **differential diagnoses?**

A. As follows:

- Tuberculosis
- Hemochromatosis
- Diabetes mellitus
- Malabsorption syndrome.

Q. What **investigations** should be done to diagnose Addison's disease?

A. As follows:

1. Routine tests:
   - CBC (shows high eosinophil, lymphocyte and ESR). Anemia may be present, specially associated with pernicious anemia
   - Blood glucose (low or lower limit, especially during Addisonian crisis)
   - Electrolytes (hyponatremia and hyperkalemia. Hyponatremia is more important than hyperkalemia. Mild acidosis may be present)
   - Other tests—serum renin (increases), aldosterone (low) and serum calcium (may be high).

2. Test to confirm:
   - Plasma ACTH and cortisol measurement is confirmatory (there is high ACTH, >80 ng/L, and low or lower normal cortisol)
   - Short synacthen test should be done. If cortisol level does not rise, it indicates primary or secondary adrenocortical deficiency. Then plasma ACTH should be done. ACTH is high in Addison's disease and low or undetectable in ACTH deficiency. If ACTH test is unavailable, then long synacthen test can be done to differentiate between primary and secondary adrenocortical deficiency. (See below).

3. Tests to find out causes:
   - Chest X-ray (to diagnose tuberculosis)
   - Plain X-ray abdomen (to see adrenal calcification in TB)
   - Adrenal auto-antibody
   - USG or CT scan of adrenals (to look for calcification in TB or malignancy).

4. Other tests:
   - Screening for pernicious anemia and other autoimmune disorders
   - Thyroid screening
   - Other tests according to suspicion of cause (e.g. sarcoidosis, amyloidosis, hemochromatosis, HIV, histoplasmosis, metastatic carcinoma, etc).

Q. How to perform **synacthen** test?

A. Short synacthen test may be done anytime of the day, but better at 9 a.m., non-fasting. It is usually done for:

1. Diagnosing Addison's disease.
2. Screening test for ACTH deficiency.

Procedure:

- Short synacthen test—250 µg ACTH (synacthen or tetracosactrin) IM or IV is given. Serum cortisol is measured at 0 and 30 minutes. If cortisol raises > 460 nmol/L, it rules out Addison's disease. Failure to rise may indicate primary or secondary adrenocortical insufficiency.
- Long synacthen test—1 mg ACTH IM daily for 3 days. Serum cortisol is measured at 0, 4, 8 and 24 hours on each day. Progressive rise of cortisol indicates secondary adrenocortical insufficiency. Failure to rise indicates Addison's disease (cortisol remains < 700 nmol/L 8 hours after last injection).

Note. Remember the following -

- If the patient is on dexamethasone or betamethasone, it will not interfere with cortisol assay (as these do not cross react).
- Random cortisol is usually low in Addison's disease, but in some cases, it may be within normal or inappropriately low in seriously ill patient. So, random cortisol measurement is of no importance. However, if random cortisol is <100 nmol/L, it is highly suggestive of Addison's disease. Also, if the serum cortisol is > 460 nmol/L, it rules out Addison's disease.
- Single test for diagnosis of Addison's disease is simultaneous measurement of ACTH and serum cortisol level (ACTH is high, cortisol is low).

Q. How to **treat** Addison's disease?

A. As follows:

1. Replacement of hormones:
   - Glucocorticoid:
     - Hydrocortisone—15 mg in morning (after waking) and 5 mg in afternoon (6 pm). According to some authority, 10 mg after waking, 5 mg at 12 noon and 5 mg at 6 pm.
     - Or, if hydrocortisone is not available, prednisolone 5 mg on waking in morning and 2.5 mg at 6 pm in afternoon.
   - Mineralocorticoid—Fludrocortisone 0.05 to 0.1 mg (50 to 300 µg) daily.
   - Androgen—Dehydroepiandrosterone (DHEA) 50 mg/day may be given in female. It increases libido and sense of well-being, but complications like acne and hirsutism may occur.

2. Treatment of the cause, as for example, antitubercular therapy in tuberculosis.

General advice to the patient:

1. The patient should always carry a bracelet and steroid card, which should contain informations regarding the diagnosis, dose of steroid and doctor's contact address.
2. Good nutrition, regular meal, high carbohydrate and sufficient salt.
3. The patient should keep ampules of hydrocortisone at home. If oral therapy is impossible, the patient should take injection by himself, family members or GP.
4. The patient should know how to increase steroid replacement dose for intercurrent illness. During intercurrent stress (fever, cold and trauma), the dose should be doubled.

Monitoring of the patient:

- Proper history regarding overall well-being
- Measurement of BP and weight
- Serum electrolyte.

Note. Remember the following points during stress -

- Intercurrent stress (fever, cold and trauma)—double dose of steroid.
- During surgery:
  - Minor surgery—hydrocortisone 100 mg IM or IV premedication.
  - Major surgery—hydrocortisone 100 mg IM or IV 6 hourly for 24 hours, then 50 mg 6 hourly. It should be continued until the patient is capable of taking by mouth.
- If gastroenteritis—IV or IM hydrocortisone should replace oral therapy.

RELATED QUESTIONS AND ANSWERS

Q. What is **Addison's disease**?

A. It is the primary adrenocortical insufficiency, resulting in glucocorticoid and mineralocorticoid insufficiency. There is destruction of the adrenal cortex.

Q. What are the **causes** of Addison's disease?

A. As follows:

1. Common causes:
- Autoimmune mechanism—80% of the cases (more in female)
- Tuberculosis of adrenal gland (in 10% cases)
- Secondary deposit in adrenals
- HIV infection
- Bilateral adrenalectomy.

2. Other causes (less common or rare):
- Amyloidosis
- Sarcoidosis
- Hemochromatosis
- Bilateral adrenal hemorrhage—following meningococcal septicemia (Waterhouse-Friedrichsen syndrome) and trauma
- Lymphoma.

Q. What are the **sites of pigmentation** in Addison's disease?

A. As follows:
- May be generalized
- Exposed parts (face, neck)
- Skin crease (palmar crease) and knuckles
- Pressure points (elbow, knee)
- Recent scar.

Q. What are the **diagnostic criteria** in Addison's disease?

A. Triad of:
- Weakness or emaciation (100% cases)
- Pigmentation (90% cases)
- Hypotension (88%)

(Other features—gastroenteritis in 56%, postural symptoms 12%, salt craving 19%).

Q. Why **postural hypotension** occurs in Addison's disease?

A. It is due to hypovolemia and sodium loss. Mineralocorticoid deficiency is responsible for hypotension.

Q. What is the size of the **heart** in Addison's disease?

A. Small heart.

Q. What **diseases are associated** with Addison's disease?

A. It is an autoimmune disease, so may be associated with other autoimmune diseases, such as—Graves' disease, Hashimoto's thyroiditis, pernicious anemia, primary ovarian failure, myasthenia gravis, type I DM etc.

Q. What are the **presentations** of Addison's disease?

A. As follows:

- Chronic adrenocortical insufficiency (weakness, pigmentation, hypotension)
- Addisonian crisis.

Q. Why **vitiligo** occurs in Addison's disease?

A. It is due to autoimmunity. Vitiligo is present in 10 to 20% cases.

Q. Why **pigmentation** occurs in Addison's disease?

A. It is due to excess ACTH that stimulates excess melanin production.

Q. How to **differentiate** between primary and secondary adrenocortical insufficiency?

A. As follows:

Primary	Secondary
1. Primary involvement of adrenal gland	Cause in pituitary or prolonged use of steroid
2. Pigmentation is present	Usually pallor
3. BP—low	BP—normal, because aldosterone secretion is not dependent on ACTH
4. Secondary sex characters are normal	Early loss of secondary sex characters. Also there are features of deficiency of other pituitary hormones
5. ACTH—high	ACTH—Low
6. Electrolytes—low Na+, high K+	Usually normal electrolytes
7. Autoimmune diseases are associated	Unlikely

Q. What is **Addisonian crisis?**

A. It is an acute severe adrenocortical insufficiency, characterized by circulatory shock with severe hypotension. It is often precipitated by intercurrent disease, surgery or infection. The patient presents with muscle cramps, nausea, vomiting, diarrhea, acute abdomen, collapse and unconsciousness. There may be unexplained fever. Laboratory findings include hyponatremia, hyperkalemia and in some cases, hypoglycemia and hypercalcemia.

Causes:

- Sudden withdrawal of steroid (common cause, if the patient on steroid for long time)
- Stress (severe infection and operation)
- Bilateral adrenal hemorrhage (meningococcal septicemia, injury and anticoagulant)
- Thyroxine therapy in a patient with hypopituitarism without steroid therapy.

Treatment:

- Blood is taken to measure cortisol, glucose and electrolytes
- Three problems are present—shortage of salt, sugar and steroid (**3S**)
- IV fluid, normal saline rapidly (1 L in 30 to 60 minutes). Subsequently, several liters of normal saline may be required in 24 hours
- IV 10% glucose
- IV hydrocortisone 100 mg stat. Then hydrocortisone 100 mg IV or IM 6 hourly, which is continued until the patient is stable and can take by mouth. Then oral steroid is started. Initially, hydrocortisone 20 mg 8 hourly, reducing to 20 to 30 mg in divided doses over a few days (then original replacement therapy should be given)
- Treatment of underlying cause (e.g. infection, adrenal or pituitary pathology, etc).

Note. Remember the following -

- In severe hyponatremia (<125 mmol/L), hypertonic saline is unnecessary, plasma Na should not be increased >10 mmol/L/day. This may cause central pontine myelinolysis (osmotic demyelination syndrome).
- During crisis or acute illness, mineralocorticoid such as fludrocortisone is unnecessary, as high dose of steroid provides sufficient mineralocorticoid activity. It can be started later on.
- For hyperkalemia, volume replacement is sufficient. No extra treatment is usually necessary, but occasionally requires specific therapy.

Q. What **drug is avoided** in acute abdominal pain in Addison's disease?

A. Morphine, as the patient is more sensitive to this drug.

HYPOPITUITARISM (DUE TO SHEEHAN'S SYNDROME)

CHIEF COMPLAINTS

- Weakness, dizziness and giddiness for … months
- Failure to breast feed for … months
- Amenorrhea for … months
- Weight loss for the same duration
- Cold intolerance and constipation for the same duration.

HISTORY

History of present illness: According to the statement of the patient, she was reasonably well … months back. Following delivery of her last baby, which was complicated by prolonged profuse vaginal bleeding, she has been suffering from severe weakness, dizziness and giddiness. She also complains of failure to breastfeed and amenorrhea since the birth of her baby. The patient also complains of significant weight loss, though her appetite is quite good. For the last --- month, she also experiences intolerance to cold and occasional constipation. She noticed hair loss and also decreased libido for the same duration. There is no history of headache, visual disturbance, convulsion, or head injury. She denies excessive thirst or polyuria.

History of past illness: Mention according to the statement of the patient.

Family history: Mention according to the statement of the patient.

Socioeconomic history: Mention according to the statement of the patient.

Menstrual history: Her menstrual period was regular prior to this incident.

Drug and treatment history: She received 5 units of blood transfusion during the bleeding episode.

GENERAL EXAMINATION

- The patient is ill looking, pale and emaciated
- Mildly anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia, edema
- No lymphadenopathy or thyromegaly
- Skin is fine and wrinkled
- There is loss of axillary and pubic hair
- Pulse: 96/min
- BP: Lying 105/70 mm Hg, standing 90/60 mm Hg
- Respiration: 14/min
- Temperature: Normal.

Examination of other systems revealed no abnormalities.

SALIENT FEATURES

Mrs. …, 33 years old, housewife, normotensive, nondiabetic, hailing from …, gave birth to her last baby … months back during which there was prolonged profuse vaginal bleeding. Since then, she has been suffering from severe weakness, dizziness and giddiness. She also complains of failure to

breastfeed and amenorrhea since the birth of her baby. The patient also complains of significant weight loss, though her appetite is quite good. For the last--month also experiences intolerance to cold and occasional constipation. She noticed hair loss and also decreased libido for the same duration. There is no history of headache, visual disturbance, convulsion, or head injury. She denies excessive thirst or polyuria. Her menstrual period was regular prior to this incident. She received 5 units of blood transfusion during the bleeding episode. She was treated with vitamins and calcium tablets. There is no history of similar illness in her family.

On Examination

General examination (mention as above).

Systemic examination (mention as above).

My diagnosis is hypopituitarism (due to Sheehan's syndrome).

Q. Why is it Sheehan's syndrome?

A. There is history of persistent prolonged severe bleeding following delivery. After that, there is failure of lactation, persistent amenorrhea and reduction of secondary sex characteristics (breast atrophy, loss of axillary and pubic hair).

Q. What are your differential diagnoses?

A. As follows:

- Addison's disease
- Diabetes mellitus.

Q. What investigations do you suggest in hypopituitarism due to Sheehan's syndrome?

A. As follows:

1. Routine: CBC with ESR, serum electrolytes, RBS.
2. Serum hormone measurement:
   - For adrenocortical insufficiency—Serum cortisol and ACTH level (if needed, synacthen test)
   - For thyroid—FT_4 (low) and TSH (usually low, may be normal or in lower limit)
   - For gonadotrophins—FSH and LH
   - GH is not routinely done. Only considered, if growth hormone replacement is possible.
3. MRI of the head to see the pituitary gland.

Note. Remember the following points:

- If hypopituitarism is due to other cause, investigate accordingly.
- Hypopituitarism in male – serum testosterone level is measured. If it is low, then FSH and LH levels are also done to differentiate between primary and secondary hypogonadism.
- Because of deficiency of ADH, the patient may develop cranial diabetes insipidus. However, the symptoms are masked due to deficiency of ACTH and glucocorticoid. Features of diabetes insipidus may appear after steroid therapy.

RELATED QUESTIONS AND ANSWERS

Q. What is Sheehan's syndrome?

A. It is a syndrome of hypopituitarism due to infarction of the pituitary gland following prolonged postpartum hemorrhage. Postpartum pituitary infarction occurs, because the enlarged pituitary gland in pregnancy is more vulnerable to ischemia after prolonged and massive postpartum hemorrhage and hypotension. Failure of lactation is the earliest symptom. Other symptoms appear over months or years.

Q. How to **treat Sheehan's syndrome?**

A. As follows:

- Hydrocortisone 15 mg in morning (after waking) and 5 mg in afternoon (6 pm). According to some authority, 10 mg after waking, 5 mg at 12 pm and 5 mg at 6 pm (If hydrocortisone is not available, prednisolone 5 mg on waking in morning and 2.5 mg at 6 pm in afternoon).
- Thyroxine 50 to 150 μg in the morning before meal.
- Sex hormone replacement (to restore sexual function and also, to prevent osteoporosis). Usually, oestrogen and androgen (DHEA) are given. Or combination of contraceptive pill may be given.
- If the patient wishes for fertility—hCG plus FSH or pulsatile GnRH may be given.
- Steroid card should be maintained.

Note. Remember the following:

- In any patient with hypopituitarism, always start first with cortisol, then thyroxine. It is dangerous to start thyroxine without first giving glucocorticoid. If thyroxine is started first without giving cortisol in adrenal deficiency, there may be adrenal crisis.
- In premenopausal women, estrogen from 1 to 21 days plus progesterone from 14 to 21 days.
- In postmenopausal women, treatment is same as premenopausal woman (in patient with hysterectomy, progesterone is not necessary).
- In male patient with hypopituitarism, testosterone (oral, IM, intradermal or implant) is given.
- In child with hypopituitarism, growth hormone replacement should be given. In adult, sometimes growth hormone replacement may be considered, if there is GH deficiency, which has effect on muscle mass and well being.

Q. What is **panhypopituitarism**? What is the **sequence** of loss of pituitary hormones in panhypopituitarism?

A. Panhypopituitarism is a syndrome produced by complete or near complete destruction of the pituitary, causing deficiency of all the pituitary hormones. It is characterized by asthenia, loss of sexual function and loss of target organ functions like thyroid, adrenal gland and gonads. In panhypopituitarism, first there is loss of growth hormone and gonadotrophin (LH and FSH), followed by ACTH, TSH.

Q. What is the common **presentation** of a patient with hypopituitarism?

A. As follows:

- Weakness, lassitude, malaise
- Loss of libido
- Absence of secondary sex characters.

Q. How to **differentiate** between Addison's disease and hypopituitarism?

A. As follows:

Addison's disease	Hypopituitarism
1. Primary involvement of adrenal gland	Cause in pituitary
2. Pigmentation present	Usually pallor
3. BP—low	BP—normal, because aldosterone secretion is not dependent on ACTH
4. Secondary sex characters are normal	Early loss of secondary sex characters. Also associated with other pituitary hormone deficiency.

5. ACTH—high	ACTH—low
6. Electrolytes—low Na+, high K+	Usually normal electrolytes.
7. Ocular sign absent.	May be present, if it is due to pituitary tumor
8. Autoimmune diseases—associated	Unlikely

Q. What are the **causes** of hypopituitarism?

A. As follows:

1. Pituitary cause:
   - ♦ Pituitary masses:
     - Pituitary adenoma, carcinoma (rare), secondaries including leukemia and lymphoma
     - Pituitary cyst
     - Pituitary granuloma (tuberculosis, syphilitic gumma)
   - ♦ Pituitary surgery (resection or removal of tumor)
   - ♦ Pituitary irradiation
   - ♦ Pituitary trauma
   - ♦ Pituitary apoplexy
   - ♦ Sheehan's syndrome
   - ♦ Infiltrative disorder—hemochromatosis, lymphocytic hypophysitis, sarcoidosis, amyloidosis
   - ♦ Others—autoimmune hypophysitis, idiopathic, congenital, Langerhans cell histiocytosis, MEN-I.
2. Extrapituitary causes:
   - ♦ Craniopharyngioma
   - ♦ Other: meningioma, germinoma, glioma, pinealoma.
3. Secondary to hypothalamic disorder.

Q. What are the **commonest cause** of hypopituitarism?

A. Pituitary tumor, surgery, radiotherapy, head injury, craniopharyngioma, meningioma.

Q. What are the causes of **coma** in hypopituitarism?

A. As follows:

- ❖ Hypoglycemia
- ❖ Hyponatremia
- ❖ Water intoxication
- ❖ Hypothyroidism
- ❖ Hypothermia.

Q. How to **treat coma** in hypopituitarism?

A. As follows:

- ❖ IV fluid (normal saline)
- ❖ IV glucose
- ❖ IV hydrocortisone 100 mg 6 hourly
- ❖ Control infection
- ❖ Thyroxine may be needed (IV triiodothyronine is preferred).

ACROMEGALY

CHIEF COMPLAINTS

- Progressive enlargement of the body for … months
- Weakness and weight gain for … months
- Change in voice for … months
- Headache for … months
- Joint pain for … months
- Excessive sweating for … months.

HISTORY

History of present illness: According to the statement of the patient, he was reasonably well … years back. Since then, he has been experiencing progressive enlargement of body, mainly his head, hands and feet. His face is also enlarged, including the jaw, leading to difficulty in chewing. He also complains of severe weakness despite significant weight gain. His voice has recently changed and become hoarse.

The patient also complains of frequent headache involving the whole head, more marked in the morning, which is not associated with nausea or vomiting. For the last … months, he is also complaining of joint pain involving both the knees, ankles and elbows. The pain is aggravated by activity and relieved by taking rest. It is not associated with morning stiffness. Recently he noticed excessive sweating even at rest. There is no history of any visual disturbance, cold intolerance, sleepiness. His bowel and bladder habits are normal.

History of past illness

Family history

Socioeconomic history

Drug and treatment history: Mention accordingly.

GENERAL EXAMINATION

- The patient looks obese with large coarse face, large jaw with widely apart teeth prominent supra-orbital ridge, increased wrinkling of the forehead and baggy eyelids. Nose, lips and ears are large
- Scalp is large (bulldog scalp)
- Hands are large, warm and sweaty with doughy feeling, fingers are spade like
- Feet are large
- Skin is thick, greasy, and sweaty (hyperhydrosis)
- Coarse body hair
- Voice is husky, cavernous
- Gynecomastia: Present
- Clubbing: Present (involving all fingers and toes)
- Thyromegaly (diffusely enlarged)
- There is no anemia, jaundice, cyanosis, koilonychia, leukonychia, edema
- Pulse: 96/min
- BP: 150/90 mm Hg
- Temperature: 99°F
- Respiratory rate: 14/min.

(There may be kyphosis, scoliosis, axillary skin tag, acanthosis nigricans).

SYSTEMIC EXAMINATION

Gastrointestinal System

- Tongue, lips and jaw are enlarged. Lower jaw is protruded with malocclusion of teeth (prognathism).
- Abdomen—hepatomegaly (may be).

Nervous System

- Voice is hoarse, husky and cavernous.
- Visual field defect—bitemporal hemianopia.

Cardiovascular System

- Cardiomegaly (evidenced by shifting of the apex beat, which is heaving).

Musculoskeletal System

- Both the knee and ankle joints, elbow joints, also joints of hands are tender, but no restricted movement.

Examination of other systems reveals normal findings.

SALIENT FEATURES

Mr. …, 46 years old, businessman, normotensive, nondiabetic, hailing from …, presented with progressive enlargement of body, mainly his head, hands and feet, for … months. His face is also enlarged, including the jaw, leading to difficulty in chewing. He also complains of severe weakness despite significant weight gain. His voice has recently changed and become hoarse. The patient also complains of frequent headache involving the whole head, more marked in the morning, which is not associated with nausea or vomiting. For the last … months, he is also complaining of joint pain involving both the knees, ankles and elbows. The pain is aggravated by activity and relieved by taking rest. It is not associated with morning stiffness. Recently he noticed excessive sweating even at rest. There is no history of any visual disturbance, cold intolerance, sleepiness. His bowel and bladder habits are normal. There is no family history of such illness. He was treated with different medicine the name of which he cannot mention.

On Examination

General examination (mention as above).

Systemic examination (mention as above).

My diagnosis is acromegaly.

Q. What are your **differential diagnoses**?

A. Hypothyroidism

Q. What **investigations** should be done in acromegaly?

A. As follows:

1. Radiology:
   - X-ray of skull (there is enlarged sella-turcica, erosion of the clinoid process, enlarged skull, mandible and sinuses, double floor sella, prognathism)

- X-ray of hands (there is large soft tissue, bones, widening of joint spaces, tufting of the terminal phalanges)
- X-ray of feet—to see heel-pad (normally, female—up to 18 mm and male—21.5 mm. If it is >25 mm—highly suggestive). Other changes like hand.
- X-ray of chest (shows enlarged heart).
- Other radiological tests like X-ray of the knee joints or other joints, if needed.

2. GH assay (radio-immunoassay)—normally, < 1 mU in adult (except in stress).
3. GTT with simultaneous measurement of GH (more diagnostic)—normally during GTT, there is suppression of GH < 2 mU. But in acromegaly, there is failure of suppression of GH, occasionally paradoxical rise of GH.
4. Measurement of IGF-1 (also called somatomedin-C)—usually increased.
5. CT scan or MRI of skull (MRI is more preferable) with gadolinium enhancement.
6. Others:
   - Assessment of other anterior pituitary hormones
   - Comparison with old photographs
   - Perimetry (to see bitemporal hemianopia)
   - Blood sugar (there is DM in 10% cases, IGT in 25% cases)
   - ECG
   - Serum calcium (increased in MEN-I).

Q. How to **treat** acromegaly?

A. As follows

1. Surgery:
   - Trans-sphenoidal removal of microadenoma is the treatment of choice (there is high success rate, rapid reduction of growth hormone and low incidence of hypopituitarism). Cure rate is 80% in microadenoma, 40% in macroadenoma.
   - After 3 months postoperative, measure growth hormone and pituitary function tests. If growth hormone remains high, adjuvant medical or radiotherapy may be needed
   - Occasionally, transfrontal surgery is done in large macroadenoma with suprasellar extension. Total removal of tumor may not be possible due to more complications. Postoperative radiotherapy should be given.
2. Radiotherapy:
   - It is used as a second line therapy. External irradiation by linear accelerator is given in acromegaly which persists after surgery, to stop the tumor growth and to lower growth hormone levels. However, growth hormone level falls very slowly over many years (previously, implantation of Yttrium was used).
   - Radiotherapy can be used in combination with somatostatin analogue or dopamine agonist, because of slow biochemical response to radiotherapy.
3. Drugs: Given if surgery is not possible or persistent acromegaly after surgery.
   - Somatostatin analogue (octreotide or lanreotide) may be used as a slow release injection, every 2 to 4 weeks.
   - Bromocriptine: It is a dopamine agonist, given in high dose, reduces GH level and the size of tumor. But it is less potent in lowering growth hormone and recurs after withdrawal of the drug. Its main side effects are nausea, vomiting and postural hypotension. Alternatively, cabergoline 0.5 mg/day may be given, or quinagolide may be used.
   - A peptide GH receptor antagonist (pegvisomant) may be used.
4. Other treatment:
   - Control of hypertension and diabetes mellitus (both improve with the treatment of acromegaly).
   - Cardiac problems—whether improves with the treatment of acromegaly is not clear.

Note. Remember the following -

Aims of treatment is to reduce the growth hormone level below 5 mU/L which shows reduced mortality. A normal IGF-1 level is also a goal of therapy. So, the progress can be assessed by monitoring growth hormone and IGF-1 level.

RELATED QUESTIONS AND ANSWERS

Q. What is acromegaly?

A. Acromegaly is characterized by generalized enlargement of the whole body, due to excess growth hormone secretion from pituitary macroadenoma (> 10 mm) after union of epiphysis. If occurs before the union of epiphysis, it is called gigantism.

Q. Why it is called acromegaly?

A. Because of the enlargement of peripheral (acral) parts of body (acral means periphery and megaly means big).

Q. Can acromegaly and gigantism exist together?

A. Yes, if excess growth hormone starts in adolescence and persists in adult life, the two conditions may be present together.

Q. What is the cause of acromegaly?

A. Eosinophilic adenoma of pituitary (macroadenoma) causing excessive GH secretion, after the fusion of the epiphysis (so there is enlargement of the soft tissue and flat bones). Very rarely, ectopic production of GHRH may cause acromegaly (in pancreatic islet cell tumor, oat cell carcinoma of bronchus, medullary carcinoma of thyroid).

Q. What are the changes in the eyes in acromegaly?

A. In the eyes:

- Visual field defect, usually bitemporal hemianopia (due to pressure on optic chiasma).
- Others—optic atrophy, papilledema, angioid streaks in retina.

Q. What are the causes of prominent supraorbital ridge?

A. As follows:

- Ricket
- Paget's disease
- Achrondroplasia
- Hydrocephalus
- Hereditary hemolytic anemia.

Q. What are the causes of macroglossia?

A. As follows:

- Acromegaly
- Hypothyroidism
- Amyloidosis
- Down's syndrome.

Q. What are the causes of baggy eyelids?

A. As follows:

- Old age
- Myxedema.

- Acromegaly
- Alcoholism
- Nephrotic syndrome or acute glomerulonephritis.

Q. What are the **presentations** of acromegaly?

A. As follows:

- Progressive increase of the size of the body (there may be history of change in size of rings, shoes, hats)
- Weight gain but weakness
- Visual field defect (the patient gives history of collision with doors, persons, because of the defective temporal field of vision)
- Headache (common)
- Excessive sweating
- Features of hypertension, diabetes mellitus
- The patient may give history of frequent visit to the dentist
- Sleep apnea syndrome.

Q. What are the signs of **active acromegaly**?

A. Signs of activity:

- Progressive increase in the size of the body
- Excessive sweating
- Increasing visual field defect
- Large skin tags (Molluscum fibrosum)
- Presence of glycosuria (diabetes mellitus)
- Hypertension
- Progressive headache
- Enlarging thyroid.

Q. What are **causes of death** in acromegaly?

A. As follows:

- Heart failure
- Complications of hypertension
- Complications of DM
- Coronary artery disease
- Tumor expansion (mass effect)
- There is an increased death due to neoplasia, especially large bowel tumor
- Pituitary apoplexy—rapid expansion of a pituitary tumor due to infarction or hemorrhage within the tumor. The patient may complain of sudden severe headache followed by loss of consciousness. Immediate neurosurgical intervention should be done.

Q. How to **assess the response** of therapy in acromegaly?

A. As follows:

- Clinical improvement (decreased facial puffiness, body size, less sweating, improvement of hypertension, DM).
- Progress can be assessed by GH and IGF-1 measurement.

Q. What are the **long term complications** of acromegaly?

A. As follows:

- Increase incidence of large bowel carcinoma
- Increase atherosclerosis.

Q. What are the causes of **hyperprolactinemia?**

A. As follows:

1. Physiological—severe stress, pregnancy, lactation, exercise, coitus, sleep.
2. Drugs:
   - Dopamine antagonist group of drugs—
     - Antipsychotic (phenothiazine, butyrophenons)
     - Antiemetic (metoclopramide, domperidone)
     - Antidepressant.
   - Dopamine depleting drugs (methyldopa).
   - Estrogen therapy (e.g. oral contraceptive pill).
3. Pathological:
   - Prolactinoma (usually microadenoma <10 mm)
   - Pituitary macroadenoma
   - Macroprolactinemia (there is high prolactin without clinical features of hyperprolactinemia)
   - Primary hypothyroidism
   - Polycystic ovarian syndrome
   - Rarely—renal failure, liver failure, hypothalamic tumor, ectopic tumor, post-ictal state, chest wall injury or reflex (e.g. postherpes zoster)
   - Idiopathic.

Clinical features of hyperprolactinemia:

- Galactorrhea, hypogonadism (commonest symptoms)
- In male—decrease libido, impotence, lethargy
- In female—amenorrhea, oligomenorrhea, menorrhagia, infertility.

Investigations:

- Serum prolactin (very high)
- CT scan or MRI of brain
- Other investigations according to the suspicion of cause, as for example, thyroid function, renal function.

Note. Remember the following points –

- If serum prolactin is high, repeat measurement is indicated to reconfirm
- If serum prolactin is 500 to 1000 mU/L, it is more likely due to stress or drugs
- If serum prolactin is 1000 to 5000 mU/L, may be due to stress or drugs or microadenoma
- Serum prolactin >5000 mU/L is highly suggestive of macroprolactinoma.

Treatment:

- Treatment of primary cause and stop the responsible drugs, if any
- Dopamine agonist drugs (such as bromocriptine, cabergoline and quinagolide) are usually given as a first line therapy
- Trans-sphenoidal surgery—may be done in microadenoma. It is also done in macroadenoma though complete removal may not be possible
- Radiotherapy—if macroadenoma fails to shrink following dopamine agonist drugs or total surgical removal is not possible
- In pregnancy, tumor size may be enlarged and may cause headache and visual field defect. In such case, dopamine agonist therapy should be started, if there are symptoms.

Indications of surgery:

- Intolerance to drugs
- Resistance to drugs
- Rapid expansion causing mass effect like visual field defect
- Large cystic macroadenoma.

DIABETES MELLITUS

CHIEF COMPLAINTS

- Weight loss and weakness for … months.
- Excessive thirst and frequent passage of urine for … months.
- Burning sensation of the hands and feet for … weeks.
- Dimness of vision for … months.

HISTORY

History of present illness: According to the statement of the patient, he was alright … months back. Since then, he has been suffering from gradual loss of weight, about 12 kg, despite good appetite. It is associated with extreme weakness and excessive thirst for which he used to take plenty of water every day. He also complains of frequency of micturition, passage of large volume of urine and waking up from sleep to void. For the last … weeks, he has been experiencing burning sensation, heaviness, tingling and numbness of both hands and feet. His vision is progressively deteriorating over the last … months. There is no history of loss of consciousness (diabetic ketoacidosis, hypoglycemia), generalized swelling of body or legs (nephropathy), chest pain (IHD), dizziness or giddiness (postural hypotension) or any skin abnormality (dermopathy, infection). He denies any history of heat intolerance, tremor (thyrotoxicosis), bowel abnormality (malabsorption), cough, hemoptysis or evening rise of temperature (TB).

History of past illness: There is no history of previous significant illness.

Family history: His father is diabetic for the last 25 years and his mother is hypertensive. He has two brothers and one sister. All of them are in good health.

Socioeconomic history: Mention accordingly.

Drug and treatment history: He is now taking tablets. Glibenclamide, 2 tablets daily.

GENERAL EXAMINATION

- Ill looking and emaciated. (look for height, weight and BMI)
- There is no anemia, jaundice, clubbing, koilonychia, leukonychia or edema
- No thyromegaly or lymphadenopathy
- There is no ulceration or skin abnormality
- Pulse—96/min (look for peripheral pulses, may be feeble)
- BP—130/80 mm Hg lying and 125/80 mm Hg standing
- Temperature—98ºF
- Respiratory rate—14/min.

SYSTEMIC EXAMINATION

Nervous System

1. Higher psychic functions: Intact.
2. Cranial nerves: Intact.
3. Motor system:

- Muscle tone diminished in the lower limbs
- Muscle power is diminished, grade 3/ 5 in the lower limbs
- There is wasting of all the groups of muscle in the feet, legs and thighs.
- Reflexes—

Jerks	Biceps	Triceps	Supinator	Knee	Ankle	Plantar
Right	Diminished	Diminished	Diminished	Diminished	Absent	Equivocal
Left	Diminished	Diminished	Diminished	Diminished	Absent	Equivocal

- Superficial reflexes (abdominal reflex)—absent
- Co-ordination—impaired in the lower limbs
- Romberg's sign—positive
- Gait—normal
- Involuntary movement—absent.

4. Sensory system:
   - Superficial sensation (pain, touch, temperature)—diminished in the foot up to mid leg and hands (glove and stocking distribution)
   - Deep sensation (vibration, position sense)—absent in both the lower limbs.
5. Cerebellar test: Normal.
6. Autonomic function: Normal, as evidenced by normal pulse, no postural hypotension.
7. Fundoscopy: Few dot and blot hemorrhages in the 6 o'clock position, 2 disc diameter away from the optic disc in the right eye. Few dot hemorrhages in 10 o'clock position, 1 disc diameter away from the optic disc.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 55 years old, businessman, diabetic, nonhypertensive, nonsmoker, hailing from …, presented with gradual loss of about 12 kg body weight, despite good appetite. It is associated with extreme weakness and excessive thirst for which he used to take plenty of water every day. He also complains of frequency of micturition, passage of large volume of urine and waking up from sleep to void. For the last … weeks, he has been experiencing burning sensation, heaviness, tingling and numbness of both hands and feet. His vision is progressively deteriorating over the last … months. There is no history of loss of consciousness, generalized swelling of body or legs, chest pain, dizziness or giddiness or any skin abnormality. He denies any history of heat intolerance, tremor, bowel abnormality, cough, hemoptysis or evening rise of temperature. There is no history of previous significant illness. His father was diabetic for 25 years, mother is hypertensive. He has two brothers and one sister; all of them are in good health. He is now taking tablet Glibenclamide, 2 tab daily.

On Examination

General examination (mention as above).

Systemic examination (mention as above).

My diagnosis is diabetes mellitus with peripheral neuropathy with diabetic retinopathy.

Q. What **investigations** do you suggest in this case?

A. As follows:

- Urine R/M/E
- Blood sugar (fasting and 2 hours after breakfast)

- HbA_{1C}
- CBC with ESR
- Blood urea and serum creatinine
- Serum lipid profile
- USG of whole abdomen
- CXR P/A view
- Plain X-ray abdomen to see pancreatic calcification
- ECG.

RELATED QUESTIONS AND ANSWERS

Q. What are the **criteria** for the diagnosis of DM?

A. Criteria for diagnosis of DM are:

- Fasting plasma venous blood sugar level > 7.0 mmol/L (or 2 hour postprandial blood sugar level > 11.1 mmol/L).
- Random blood sugar > 11.1 mmol/L.
- During OGTT, > 11.1 mmol/L 2 hour after 75 g glucose.

Note. Remember the following points:

- Random means without regard to time since the last meal
- Fasting means no calorie intake for 8 hours at least (not more than 16 hours)
- FBS (fasting blood glucose) < 5.6 mmol/L is normal
- In symptomatic patient, one abnormal finding is diagnostic of diabetes mellitus
- In asymptomatic patients, 2 values are required
- For OGTT, only fasting glucose and 2 hours after 75 glucose is sufficient for diagnosis
- OGTT should be done only in borderline cases (fasting glucose 6.1 to 7.0 mmol/L or random glucose 7.8 to 11.0 mmol/L) and also for the diagnosis of gestational diabetes mellitus.

Q. What is **impaired glucose tolerance (IGT)?**

A. When fasting glucose is less than 7 mmol, but during OGTT, 2 hours after the glucose load is 7.8 to 11.0 mmol, it is called IGT. The patient who has IGT are at increased risk of developing frank DM type 2 with time and also macrovascular complications are more (mainly cardiovascular).

Lifestyle modification for type 2 DM and annual check-up for glucose are recommended for this patient. Cardiovascular risk factors should be treated aggressively.

Q. What is **impaired fasting glucose (IFG)**?

A. IFG is defined as the fasting glucose level between 6.1 to 6.9 mmol/L (110 to 125 mg/dL) according to WHO. However, ADA defines it as fasting glucose level between 5.6 to 6.9 mmol/L (100 to 125 mg/dL). These patients are prone to develop frank diabetes mellitus and cardiovascular disease. The patient is advised for weight reduction about 5 to 10% of their body weight, regular exercise and follow up. Usually no drug therapy is recommended.

Note. Remember the following -

Patients with IGT and/or IFG are now regarded as **prediabetes**.

Q. What is **latent diabetes?**

A. It means blood glucose is usually normal, but may be high under certain stressful conditions. Examples are - pregnancy, infection, obesity, stress or drugs like steroid, thiazide diuretics, etc.

Q. What is **potential** diabetes?

A. It means blood sugar usually is normal, but the patient has increased risk of developing diabetes mellitus in future due to genetic reasons like:

- Both parents are diabetic
- One parent is diabetic and the other has family history of diabetes
- Has a diabetic sibling
- In a twin, if one is diabetic.

Q. What is **brittle diabetes?**

A. Brittle diabetes (or unstable diabetes or labile diabetes) refers to uncontrolled insulin dependent diabetes mellitus with recurrent, dramatic, large swings in blood glucose levels, often without any apparent reason. This leads to irregular and unpredictable hyperglycemia, frequently with ketosis, and sometimes serious hypoglycemia.

Brittle diabetes occurs in 1 to 2% of diabetics, usually in young (age 15 to 30 years) patient with type 1 diabetes mellitus, but may also be found in elderly patient with type 1 or type 2 diabetes mellitus. It often develops after total pancreatectomy. It may be caused by gastrointestinal absorption problems including delayed stomach emptying (gastroparesis), drug interactions, problem with insulin absorption or hormonal malfunction.

Q. What is the **Aetiological classification** of DM?

A. As follows:

1. Type 1 DM:
   - Idiopathic
   - Immune mediated
2. Type 2 DM
3. Gestational DM
4. Other specific types:
   - Genetic defects of β cell function
   - Genetic defects of insulin action
   - Genetic syndromes such as Down's syndrome, Klinefelters' syndrome, Turner's syndrome and DIDMOAD syndrome
   - Pancreatic diseases such as chronic pancreatitis and hemochromatosis
   - Endocrine diseases such as acromegaly, Cushing's syndrome, glucagonoma and thyrotoxicosis
   - Drug induced (e.g. corticosteroid)
   - Viral infections (e.g. congenital rubella, mumps and Coxsackie virus B)
   - Uncommon form of immune-mediated DM.

Q. What is **gestational diabetes mellitus (GDM)?** How is it **diagnosed**?

A. It is defined as any degree of glucose intolerance with the onset or first recognition during pregnancy. It constitutes 90% of women with pregnancy complicated by diabetes. More than 50% women ultimately develop diabetes in the next 20 years and this is linked with obesity. Mostly they develop type 2 DM.

OGTT with 75 g glucose is used as screening test for GDM for women between 24 and 28 weeks of gestation. Blood glucose is measured at fasting, 1 hour and 2 hours after glucose load. GDM is diagnosed if blood glucose is:

- Fasting > 5.1 mmol/L
- After 1 hour 10 mmol/L
- After 2 hour 8.5 mmol/L.

Q. What are the complications of **fetus** in DM during pregnancy?

A. As follows:

- Teratogenicity (if DM is present in early pregnancy, in the first 6 weeks), there may be cardiac, renal and skeletal malformations, characteristically caudal regression syndrome, neural tube defect
- Fetal macrosomia (if DM is present in later pregnancy)
- Neonatal hypoglycemia (as maternal glucose crosses the placenta, but insulin cannot. As a result, fetal islet cells secrete excess insulin, which may cause neonatal hypoglycemia)
- Increased risk of polycythemia, hyperbilirubinemia and hypocalcemia
- Hyaline membrane disease.

Q. What is the cause of **macrosomia** in DM?

A. Macrosomia means large or big baby (birth weight > 90 percentile for gestational age). It is due to persistent maternal hyperglycemia leading to fetal hyperglycemia and prolonged fetal hyperinsulinism. This stimulates excessive somatic growth mediated by insulin like growth factors (IGFs). Macrosomia affects all organs except the brain.

Q. What are the **complications** of DM?

A. As follows:

I. Acute complications:
   - Hypoglycemia
   - Diabetic ketoacidosis
   - Hyperosmolar nonketotic diabetic coma
   - Lactic acidosis
   - Infections—boils, carbuncle, abscess, cellulitis, tuberculosis.

II. Long-term complications:
   - Microvascular—
     - Neuropathy—peripheral neuropathy (sensory, motor or mixed), mononeuritis multiplex, mononeuropathy, autonomic neuropathy
     - Nephropathy (CKD)
     - Eye complications (retinopathy, cataract)
     - Foot complications (ulcers, gangrene, arthropathy).
   - Macrovascular—
     - Coronary circulation—myocardial ischemia, infarction
     - Cerebral circulation—TIA, CVD
     - Peripheral circulation—ischemia, claudication
     - Foot complications (ulcers, gangrene, arthropathy).

Note. Remember the following -

Diabetes mellitus can cause painless or silent myocardial infarction. Foot complications are due to both macro and micro vascular lesions.

Q. What are the causes of **painless myocardial infarction**?

A. As follows:

- Diabetes mellitus with autonomic neuropathy
- Elderly patient with dementia
- CVD.

Q. What are the causes of **sudden death** in diabetes mellitus?

A. It is more likely due to autonomic neuropathy. The patient usually die from sudden cardiorespiratory arrest.

Q. What are **dawn phenomenon** and **Somogyi phenomenon?**

A. As follows:

- Dawn phenomenon or effect is defined as an abnormal early morning (between 3 am to 7 am) increase in the blood sugar level in a patient with diabetes mellitus (mainly type 1). During sleep, there is a surge of secretion of counter regulatory hormones like cortisol, glucagon, growth hormone and catecholamines, which cause release of glucose from liver and increase insulin resistance leading to hyperglycemia. It is often related to insufficient insulin dosage at night and may require increasing the night dose of insulin. The patient should be advised to avoid taking carbohydrate at bedtime.
- Somogyi phenomenon or effect is defined as pre-breakfast hyperglycemia, which follows nocturnal hypoglycemia (which often goes unrecognized) that leads to increased release of counter regulatory hormones that produce high blood glucose. In this case, the previous night insulin dose is often higher than required. It is commonly seen in children. Treatment is by decreasing the overnight insulin dose.

To differentiate between dawn and Somogyi phenomenon, an early morning (3 am) and morning (fasting) blood sugar level is measured. In dawn phenomenon, both samples show hyperglycemia. In Somogyi phenomenon (3 am) blood sample shows hypoglycemia and the morning fasting blood level shows hyperglycemia.

Q. What are the **features** of **autonomic neuropathy** in DM?

A. In both type 1 and 2 DM, there may be autonomic neuropathy, which involves multiple systems of the body. Features are:

- CVS—postural hypotension, fixed heart rate, resting tachycardia and sometimes, sudden death.
- GIT—gastroparesis and nocturnal diarrhea, constipation.
- Genitourinary—urinary incontinence, difficulty in micturition, erectile dysfunction and retrograde ejaculation.
- Sudomotor—gustatory sweating, nocturnal sweating without hypoglycemia, hyperhydrosis of upper extremity and anhydrosis of lower extremity, and anhydrosis of foot can cause cracked skin and ulcer.
- Vasomotor—cold feet due to loss of vasomotor response, dependent edema due to loss of vasomotor tone and increased vascular permeability.
- Autonomic neuropathy can reduce counter-regulatory hormone release, leading to an inability to sense hypoglycemia appropriately.
- Pupillary—decreased pupil size, resistance to mydriatic and delayed or no reflex to light (called pseudo-Argyll Robertson pupil).

Q. What is **insulin resistance syndrome** or **metabolic syndrome** or **syndrome X**?

A. Presence of type 2 DM, central obesity, hypertension and dyslipidemia (elevated LDL and triglyceride, low HDL) is called metabolic syndrome. Other features are hyperinsulinemia, microalbuminuria, elevated fibrinogen and plasminogen activator inhibitor 1, plasma uric acid and increased sympathetic activity. The primary defect is insulin resistance. This predisposes to an increased risk of cardiovascular disease.

Q. What are the **types of neuropathy** in DM?

A. As follows:

- Sensory neuropathy (common)
- Mixed motor and sensory neuropathy
- Asymmetrical motor neuropathy (diabetic amyotrophy)
- Autonomic neuropathy
- Mononeuropathy
- Mononeuritis multiplex.

Mechanism of neuropathy in DM:

- Axonal degeneration
- Patchy or segmental demyelination
- Involvement of intraneural capillaries.

Q. What is **diabetic amyotrophy**?

A. A type of motor neuropathy in diabetic patient, characterized by asymmetrical wasting of muscles, usually involving the quadriceps (also in upper limb). Affected area may be tender, commonly accompanied by severe pain in anterior aspect of thigh. It may be the first presentation of DM. The patient is occasionally cachexic (neuropathic cachexia) and extremely ill, unable to get out of bed. Hyperesthesia or paresthesia is common. There is reduction of muscle power, tone, loss of knee jerk with occasional extensor plantar response on the affected side. CSF protein is increased.

Q. Where is the **site of lesion** or **cause** of diabetic amyotrophy?

A. It is probably due to acute infarction of lower motor neuron of lumbosacral plexus.

Q. How to **treat** diabetic amyotrophy?

A. As follows:

- Good control of DM
- Intensive insulin therapy
- For pain—amitriptyline, imipramine or carbamazepine. Aldose reductase inhibitor may help.

Q. What is the **prognosis**?

A. Prognosis is good, usually recovers, but may take a long time (over months to 2 years).

Q. What are the causes of **loss of vision** in DM?

A. As follows:

- Diabetic retinopathy
- Cataract
- Age-related macular degeneration
- Retinal vein occlusion
- Retinal artery occlusion
- Nonarteritic ischemic optic neuropathy
- Glaucoma.

Q. What are the **causes of unilateral wasting** of leg?

A. As follows:

- Diabetic amyotrophy
- Old poliomyelitis
- Arthritis or trauma
- Cerebral palsy
- Disc prolapse.

Q. What are the **causes** of ulcer in DM?

A. As follows:

- Ischemia
- Neuropathy
- Combined ischemia and neuropathy
- Secondary infection.

Q. What is the **pathology** of ischemic ulcer?

A. As follows:

- Usually microangiopathy
- Associated atherosclerosis of large and medium vessels.

Note. Remember the following -

If the ulcer is painful, the cause is vasculitis and if it is painless, the cause is neuropathy.

Q. How to **treat** a case of diabetic ulcer?

A. As follows:

- Good control of diabetes mellitus
- Local dressing. Avoid weight bearing
- Antibiotic to control secondary infection
- Avoid bare foot, tight shoes and smoking
- Consult with chiropodist
- Surgery may be required (amputation or angioplasty).

Causes of neuropathic ulcer:

- Leprosy
- Diabetes mellitus
- Polyneuropathy (due to any cause)
- Tabes dorsalis
- Syringomyelia
- Amyloidosis
- Porphyria
- Progressive sensory neuropathy.

Q. What are the **differences** between ischemic ulcer and neuropathic ulcer?

A. As follows:

Features	Neuropathic ulcer	Ischemic ulcer (arterial)
1. Area	Warm, dry and pink	Cold, shiny, atrophy and loss of hair
2. Pulse	Bounding	Absent or reduced
3. Sensation	Reduced or absent	Normal
4. Ulcer	Painless and mostly plantar	Painful, over heels and toes
5. Edema	Localised (may be present)	Absent (dry)
6. Reflex	Reduced or absent, equivocal plantar response	Normal

Q. What are the differences between **diabetic ketoacidosis (DKA) and hyperosmolar nonketotic diabetic coma (HNDC)?**

A. As follows:

Points	DKA	HNDC
1. Age	Young, may be any age	Elderly, >40 yrs
2. Precipitating factors	Insulin deficiency (common in type 1)	Partial insulin deficiency (common in type 2)
3. Breath	Acetone present	Absent
4. Kussmaul's breathing	Present	Absent
5. Sodium	Low	High
6. Bicarbonate	Low	Normal
7. pH	6.8 to 7.3	> 7.3
8. Ketonuria	Present	Absent
9. Osmolality	Normal	High
10. Blood glucose	High	Very high
11. Mortality	5 to 10%	30 to 40%

Q. What are the differences between **diabetic ketoacidosis and lactic acidosis?**

A. As follows:

Points	DKA	Lactic acidosis
1. Precipitating factors	Insulin deficiency, infection (not biguanide)	Biguanide
2. Dehydration	Present	Absent
3. Breath	Acetone present	Absent
4. Ketonuria	Present	Absent or mild
5. Serum lactate	Normal	High >5 mmol/L
6. Mortality	5 to 10%	>50%

Q. What is **hyperosmolar nonketotic diabetic coma (HNDC)**? Why **no ketoacidosis** in such case?

A. It is characterized by very high blood glucose (>50 mmol/L) and high plasma osmolality without ketosis. Here insulin deficiency is partial and low level of endogenous insulin is present, which is sufficient to inhibit hepatic ketogenesis, but insufficient to control hyperglycemia. It may be the first presentation of diabetes mellitus. It is common in elderly with NIDDM.

Common precipitating factors are:

- Consumption of glucose rich diet or fruits
- Concurrent medication like thiazide or steroid
- Myocardial infarction
- Intercurrent illness.

Serum osmolarity is extremely high. The resultant high osmolarity can cause cerebral damage. The patient is extremely sensitive to insulin. Hyperchloremic mild acidosis may be present due to

starvation, increased lactic acid and retention of inorganic acid. Plasma sodium is usually high (may be false low due to pseudohyponatremia). There may be high BUN, urea, creatinine and serum osmolality may be very high. Mortality rate may be up to 40%.

Treatment:

- IV 1/2 strength saline (0.45%) should be given. When osmolality is normal, 0.9% normal saline should be given. However, if hypovolemia is present as evidenced by hypotension and oliguria, 0.9% saline may be given. Usually 4 to 6 liters fluid may be required in first 8 to 10 hours.
- When glucose is 250 mg/dL, fluid replacement should include 5% dextrose in either aqua or 0.45% saline or 0.9% saline. Rate of glucose infusion should be adjusted to maintain glucose level between 250 to 300 mg/dL in order to reduce the risk of cerebral edema. When the urinary output is 50 ml/hr or more, IV fluid may be stopped.
- Low dose soluble insulin (preferably with insulin pump, 2 to 6 units hourly). Insulin dose is adjusted to reduce the glucose level by 50 to 70 mg/dL/h.
- Other treatment: NG tube feeding, catheter if needed, antibiotic if infection, correction of electrolytes, low dose heparin (as thrombosis is common).

Read the following in relation to metabolic acidosis:

Causes of metabolic acidosis with normal anion gap are:

- Renal tubular acidosis
- Diarrhea
- Ureterosigmoidostomy
- Acetazolamide therapy
- Ammonium chloride ingestion.

Causes of metabolic acidosis with high anion gap:

- Diabetic ketoacidosis
- Renal failure
- Lactic acidosis
- Salicylate poisoning.

Anion gap is calculated by $(Na + K) - (Cl + HCO_3)$ in mmol/L. Normal value is 8 to 14 mmol/L.

Osmolality is calculated by $2 \times Na + 2 \times K$ + plasma glucose + plasma urea (all in mmol/L). Normal osmolarity is 285 to 300 mosm/kg. If it is > 340 mosm, consciousness is depressed.

Q. What are the **differences** between hypoglycemic coma and diabetic coma (coma with ketoacidosis)?

A. As follows:

Points	Hypoglycemic coma	Diabetic coma (DKA)
1. History	Excess insulin, but no or insufficient food intake, following heavy exercise	Too little or no insulin, concurrent infection or digestive disturbance
2. Onset	Rapid onset, usually after taking insulin. Patient is in good health prior to this	Slow onset, the patient has ill health for several days
3. Symptoms	Weakness, tremor, sweating, palpitation, hunger, occasional vomiting from depot insulin	Intense thirst, polyuria, dehydration, vomiting, air hunger and abdominal pain

4. Signs		
» Skin and tongue	» Moist	» Dry
» Eyes	» Normal	» Sunken
» Pulse	» High volume, tachycardia	» Weak
» BP	» Normal or raised	» Low
» Breathing	» Shallow or normal	» Kussmaul's breathing
» Acetone smell	» Absent	» Present
» Reflexes	» Brisk	» Diminished
» Plantar response	» Often extensor	» Usually flexor
» Intraocular pressure	» Normal	» Decreased
5. Urine		
» Ketonuria	» Absent	» Present
» Glycosuria	» Absent	» Present
6. Blood	»	
» Glucose	» Hypoglycemia (< 60 mg/dL)	» Hyperglycemia (> 300 mg/dL)
» Bicarbonate	» Normal	» Reduced
» pH	» Normal	» Low
» Acetone	» Normal	» High
7. Treatment	Oral or IV glucose	Insulin and others
8. Prognosis	Good	Bad

Q. How to diagnose clinically a case of **hypoglycemic coma** and **hyperglycemic coma**?

A. Typical features of hypoglycemic coma are:

- Excessive sweating
- Tachycardia
- Tremor
- Other—Jerks may be brisk, planter—bilaterally extensor.

Typical features of hyperglycemic coma are:

- Severe dehydration
- Pulse—weak, BP—low
- Air-hunger is present—Kussmaul's breathing and acetone in the breath are present
- Others—Reflexes are reduced, planter will be flexor.

OBESITY

CHIEF COMPLAINTS

- Weight gain for … years.

HISTORY

History of present illness: According to the statement of the patient, though he is apparently well, but complaining of gaining weight for the last … years. His food intake is normal, not taking any excessive food or sweet. There is no history of intolerance to cold, weakness, constipation or excessive sleep. On query, there is no history of taking any drug.

History of past illness: Nothing significant

Family history: His father is normal but mother is slightly obese. He has two brothers and one sister. All are normal.

Personal history: He is a service holder, working mostly in his office which does not involve physical exertion. He is a nonsmoker and non-alcoholic.

Socioeconomic history: He is from a middle class family.

Drug and treatment history: He does not take any drug.

GENERAL EXAMINATION

- The patient looks obese involving central as well as peripheral parts of the body. Face is rounded, moon shaped but not plethoric.
- Height is 170 cm, weight is 120 kg, BMI is 41.52 kg/m^2 .
- There is no anemia, jaundice, clubbing, koilonychia, leukonychia or edema.
- No thyromegaly or lymphadenopathy.
- There are multiple linear striae involving abdomen, thighs and shoulders. No bruise.
- No proximal myopathy.
- Both breasts are enlarged (bilateral lipomastia).
- Pulse– 84/min.
- BP–130/80 mm Hg lying and 125/80 mm Hg standing.
- Temperature – 99ºF.
- Respiratory rate –14/min.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 42 years, service holder, normotensive, nondiabetic, nonsmoker, hailing from …, presented with the complaints of gaining of weight for the last … years. His food intake is normal, not taking any excessive food or sweet. There is no history of intolerance to cold, weakness, constipation or excessive sleep. On query, there is no history of taking any drug. There is no family history of similar illness.

On Examination

General examination (mention as above).

Systemic examination (mention as above).

My diagnosis is primary obesity.

Q. What are the **differential diagnoses** of simple obesity?

A. As follows:

- Hypothyroidism
- Cushing's syndrome
- Metabolic syndrome.

Q. Why **not** this is hypothyroidism?

A. In the history, there is no cold intolerance, sleepiness, lethargy, etc. There is no nonpitting edema, no coarse puffy face, no slow relaxation of the ankle jerk.

Q. Why **not** this is Cushing's syndrome?

A. In Cushing's syndrome, there is usually central obesity with relatively thin limbs, plethoric moon face, multiple purple striae, proximal muscular weakness, etc. All are absent in this case.

RELATED QUESTIONS AND ANSWERS

Q. What is **obesity**?

A. It is defined as excessive accumulation of fat, classically when the BMI is > 30 kg/m^2. It is diagnosed by the following:

- Measuring weight
- BMI
- Skin fold thickness over the middle of the triceps. Normal values are 20 mm in men and 30 mm in women
- Waist or hip circumference ratio of > 1.0 in men and > 0.9 in women (central distribution of body fat), indicates obesity.

It is associated with a higher risk of morbidity and mortality.

Q. What are the **causes** of obesity?

A. There are multiple factors:

1. Physical inactivity
2. Genetic
3. Excessive food intake
4. Psychological factors
5. Drugs—steroid, oral contraceptive pill, sodium valproate, TCA
6. Secondary disease:
   - Endocrine causes – hypothyroidism, Cushing's syndrome, insulinoma.
   - PCOS in female.
   - Hypothalamic disorder (tumors, injury). This causes polyphagia and obesity.
   - Metabolic syndrome.
   - Genetic syndrome – Laurence-Moon-Biedle syndrome, Prader-Willi syndrome.
   - Others—Pickwickian syndrome, Alstrom syndrome.

Q. What are the **reversible conditions** in obesity?

A. Hypothyroidism, Cushing's syndrome, insulinoma, hypothalamic disorder.

Q. What are the syndrome in which obesity is a **predominant feature?**

A. Cushing syndrome, Laurence-Moon-Biedle syndrome, Prader-Willi syndrome, Pickwickian syndrome, Alstrom's syndrome, PCOS.

Q. What is the **link** between obesity and diabetes mellitus?

A. Fat cells release free fatty acids and also TNF-α which are responsible for insulin resistance. A new protein called resistin secreted by the fat cells, also causes insulin resistance.

Q. What are the **mechanism** of obesity?

A. As follows:

- Insensitivity to leptin presumably in hypothalamus.
- Neuropeptide Y induced hyperphagia.
- Deficiency of production or action of anorexigenic hypothalamic neuropeptides.
- Increased secretion of insulin and glucocorticoids.
- Mutation in the gene of PPAR-γ accelerates differentiation of adipocyte and may cause obesity.

Q. What are the **complications** of obesity?

A. As follows:

- Psychological – Low self esteem, depression.
- Mechanical – Osteoarthritis of knee and hips, back strain, varicose veins, urinary incontinence, hiatus hernia, abdominal hernia, flat foot.
- Hepatobiliary – Non-alcoholic steatohepatitis, cirrhosis, gallstones.
- Respiratory – Exertional dyspnea, obstructive sleep apnea, Pickwickian syndrome.
- Cardiovascular – Hypertension, atherosclerosis, ischemic heart disease, heart failure, thrombo-embolism.
- Stroke
- Metabolic – Diabetes mellitus (type 2), hyperlipidemia, atherosclerosis, hyperuricemia and gout.
- Increased cancer risk – breast, uterus, colorectal, prostate, ovary.
- Skin infection – groin and submammary candidiasis.
- Menstrual abnormalities.
- Increased morbidity and mortality.
- Postoperative problems.
- Accident proneness.

Q. What is the **classification (or grading)** of obesity?

A. It is done according to BMI (kg/m^2):

1. Normal – 18.5 to 24.9
2. Overweight – 25 to 29.9 (mildly increased risk of co-morbidities).
3. Obese – >30, this is again divided in 3 classes according to BMI –
   a. Class I – 30 to 35 (moderate risk of co-morbidities).
   b. Class II – 35 to 40 (severe risk of co-morbidities).
   c. Class III – > 40 (very severe risk of co-morbidities).

Q. What is **BMI**?

A. Body mass index is a measure to determine the excessive adipose tissue. It is calculated as weight in kg divided by height in $meter^2$. Normal BMI is 18.5 to 24.9 kg/m^2.

Q. What is **morbid obesity**?

A. If the relative weight is > 200% (BMI > 40 kg/m^2), it is called morbid obesity. It is associated with 10 fold increase in mortality.

Q. How to **investigate** a case of obesity?

A. In any case of obesity, detail history of the patient, specially dietary history, physical activity or sedentary work, any drug, alcohol should be taken. Whether the weight gain is recent or rapid (to

exclude secondary disease like Cushing's syndrome or hypothyroidism). Then following routine investigations should be done:

- Fasting blood sugar
- Lipid profile
- Thyroid function test (FT_3, FT_4, TSH)
- Investigate for Cushing's syndrome
- Liver function test (transaminase, USG of hepatobiliary system to see fatty liver)
- X-ray chest, ECG, echocardiography – to see cardiac status
- Lung function test for sleep apnea
- X-ray of the individual joints in osteoarthrosis
- In female, if PCOS is suspected, investigate accordingly (such as USG of ovary, serum FSH and LH).

Q. How to **treat** a patient with simple obesity?

A. Multidisciplinary approach including:

- Hypocaloric diets
- Exercise
- Social support
- Avoidance of drugs, smoking, alcohol
- Treatment of secondary cause
- Drug treatment:
  - Sibutramine (it blocks serotonergic pathways)
  - Orlistat (pancreatic and gastric lipase inhibitor). It inhibits dietary fat absorption
  - Incretins (Glucagon like peptide 1)
  - Biguanide like metformin

  (Other drugs like phenfluramine, amphetamine, phentarmine, etc. are not recommended).
- Surgical management:
  - Bariatric surgery—to reduce the size of stomach.
  - Cosmetic surgery (liposuction).

Q. What are the **indication of surgery?**

A. In some cases of morbid obesity (BMI >40 kg/m^2) or BMI > 35 kg/m^2 and obesity related complications, after conventional treatment have failed.

SHORT STATURE

CHIEF COMPLAINTS

- Failure to increase in height.

HISTORY

History of present illness: According to the statement of the patient's mother, though the patient is of 20 years old, he has failed to attain adequate growth as much as his classmates and other children. There is no record regarding pregnancy of his mother. There is no history of weight gain, drug intake, long standing diarrhea, feeding problem, cold intolerance, constipation or any systemic disease. His eating habit is normal. There is no abnormality regarding bowel and bladder habits.

History of past illness: No history of any significant past illness.

Family history: His parents have normal height. He has one brother and one sister who have normal height for their age.

Socioeconomic history: He is a college student. His academic performance is good.

Drug and treatment history: He did not take any drugs.

GENERAL EXAMINATION

- The patient looks short. His height is … feet. The limbs are proportionately short.
- There is no anemia, jaundice, clubbing, koilonychia, leukonychia or edema.
- No thyromegaly or lymphadenopathy.
- Skin is normal.
- Pulse– 80/min.
- BP–120/75 mm Hg lying and 115/75 mm Hg standing.
- Temperature – 98ºF.
- Respiratory rate –14/min.
- Any features of hypogonadism (axillary or pubic hair, testicular volume, stretched penile length, Tanner stage).

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr. …, 20 years old, a student, normotensive, nondiabetic presented with failure of attaining adequate growth. There is no record regarding pregnancy of his mother. There is no history of weight gain, drug intake, long standing diarrhea, feeding problem, cold intolerance, constipation or any systemic disease. His eating habit is normal. There is no abnormality regarding bowel and bladder habits. There is no history of any significant past illness. His parents have normal height. He has one brother and one sister who have normal height for their age. He is a college student. His academic performance is good. He did not take any drugs.

On Examination

General examination (mention as above)

Systemic examination (mention as above).

My diagnosis is short stature (with or without delayed puberty).

Q. What are the **differential diagnoses** of short stature?

A. As follows:

- Familial
- Turner's syndrome
- Cretinism
- Hypopituitarism
- Isolated growth hormone deficiency.

Q. What do you think **the cause** in your case?

A. Constitutional or hypopituitarism.

Q. **Why not** hypopituitarism?

A. Because, secondary sexual characters are normal.

Q. **Why not** hypothyroidism?

A. There is no history of weight gain, cold intolerance, increased sleepiness, constipation.

RELATED QUESTIONS AND ANSWERS

Q. What are the **causes** of short stature?

A. As follows:

1. Constitutional (the commonest cause)
2. Familial or genetic
3. Physiological growth delay
4. Emotional deprivation and psychological factors
5. Chronic systemic disease:
   - Cardiac – congenital cyanotic heart disease like Fallot's tetralogy
   - Renal – Renal failure, renal tubular acidosis
   - Respiratory – Brochiectasis, brochial asthma
   - GIT – Small bowel disease like celiac disease, Hirschsprung's disease
   - Cystic fibrosis.
6. Endocrine diseases:
   - Hypopituitarism (pituitary dwarfism)
   - Isolated GH deficiency
   - Cretinism (hypothyroidism)
   - Cushing's syndrome
   - Pseudohypoparathyroidism (characterized by short stature, round face, mental retardation, epileptic attack, basal ganglia and subcutaneous calcification, short metacarpal. Hypoparathyroidism is due to defect in end organ resistance to parathormone)
   - Pseudopseudohypoparathyroidism
   - Uncontrolled Juvenile diabetes mellitus.
7. Nutritional:
   - Protein energy malnutrition like marasmus and Kwashiorkor
   - Ricket.
8. Chromosomal or genetic abnormalities:
   - Down's syndrome
   - Turner's syndrome

- Noonan's syndrome (male Turner)
- Prader-Willi syndrome
- Laurence-Moon-Biedl syndrome.

9. Skeletal dysplasia:
   - If there is short limb and normal trunk, may be due to achondroplasia
   - If there is short limb and short spine, may be due to mucopolysaccharidoses (Hurler's syndrome or Gargoylism).
10. Gross kyphoscoliosis
11. Drugs like steroid.

Q. How to **investigate** short stature?

A. A detailed history should be taken and the patient should be examined to exclude systemic diseases. It should be done as follows:

1. History to be taken:
   - Family history (parents and relatives)
   - Pregnancy record (growth retardation and weight at birth, and any congenital disease)
   - Rate of growth
   - Comparison with peers at school and siblings
   - Systemic disease (respiratory, cardiac, GIT and renal)
   - Nutrition (less intake and malabsorption)
   - Age of appearance of secondary sexual characters (pubic hair, breast, menarche)
   - Use of steroid during childhood
   - Psychosocial deprivation.
2. Physical examination:
   - Height and weight chart (if height is below third percentile, it is considered as short stature)
   - Arm span and height (achondroplasia)
   - Short limbs compared to trunk (achondroplasia)
   - Reduction of weight and height (malnutrition and systemic disease)
   - More weight but short height indicates endocrine disease (hypothyroidism, Cushing's syndrome), and genetic syndrome (Prader-Willi syndrome, Laurence-Moon-Biedl syndrome)
   - Grading of secondary sexual characteristics
   - Look for evidence of systemic disease (heart, kidney and respiratory)
   - Others (Turner's syndrome, Noonan's syndrome and pseudohypoparathyroidism).

After exclusion of systemic disease, proceed as follows:

1. Thyroid function test—serum TSH and FT_4 to exclude hypothyroidism.
2. GH status:
   - GH response to insulin is the gold standard.
   - Blood level of insulin like growth factor 1 (IGF-1) and insulin like growth factor binding protein 3 (IGF-BP3) may provide evidence of GH under secretion.
   - Basal growth hormone level is of little value. Urinary growth hormone level may be used as a screening.
3. Bone age—non-dominant hand and wrist X-rays for the assessment of bone age by comparison with standard charts.
4. Lateral skull X-ray (may show calcification—in craniopharyngioma).
5. Karyotyping in females—to exclude Turner's syndrome.
6. Other tests according to suspicion of causes.

Q. What is **dwarfism**?

A. Dwarfism may be defined as condition where the height of a person is much below the normal according to the chronological age.

Body ratio in dwarfism:

1. If upper and lower segments are equal, the causes are –
   - Hereditary
   - Constitutional
   - Pituitary dwarfism.
2. If upper segment is bigger than lower segment, the causes are –
   - Achondroplasia
   - Cretinism
   - Juvenile myxedema.
3. If upper segment is smaller than lower segment, the causes are –
   - Spinal deformity.

Q. How to **treat?**

A. As follows:

- Any systemic disease should be treated accordingly
- Nutritional supplementation
- Psychological support
- In growth hormone deficiency—recombinant growth hormone (somatropin) is given.

MULTIPLE ENDOCRINE NEOPLASIA (MEN)

CASE 1

Chief Complaints

- Excessive thirst and urination for … months
- Lethargy, depression, and nausea for … months
- Abdominal pain, heart burn and diarrhea for … months
- Swelling of right mid arm for … months
- Recurrent dizzy spells for … month.

HISTORY

History of present illness: The patient state that she was well about … months back. Since then, she has been suffering from excessive thirst and urine output, which are present throughout day and night. She also complains of abdominal pain, nausea and occasional vomiting. The pain is mostly in upper abdomen, burning in nature, improves after taking food, antacid but there is no radiation. She also complains of watery diarrhea but no mucus or blood. About 2 months back, she had fracture of her right arm following fall from standing height. For the last 1 month, she is complaining of repeated dizzy spells after prolonged fast, during exercise or on awakening from sleep. It improves after taking food in every time. There is no history of weight loss, fever, chest pain.

History of past illness: No history of any significant past illness.

Family history: Her mother had neck surgery. Other family members are in good health.

Socioeconomic history: She is a house wife.

Drug and treatment history: The patient consulted with orthopedic surgeon for fracture and was managed by conservative treatment. Currently she is taking omeprazole and antacids.

Menstrual History: The patient is amenorrheic for 2 months. Previously cycle was regular.

GENERAL EXAMINATION

- Appearance: Ill looking
- Built: Average
- BMI: 25kg/m^2
- Mildly anemic, there is no jaundice, clubbing, koilonychia, leukonychia or edema
- No thyromegaly or lymphadenopathy
- Skin is normal
- Dehydration is mild
- There is plaster cast over right arm
- Pulse: 84 min regular
- BP:145/95 mm Hg.

SYSTEMIC EXAMINATION

- Mental status—mood is depressed.
- Abdomen—epigastric tenderness is present, otherwise normal.
- All other systemic examinations reveal no abnormalities.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mrs. …, a 40-year-old, hypertensive, house wife presented with the complaints of excessive thirst and urine output, which are present throughout day and night. She also complains of abdominal pain, nausea and occasional vomiting. The pain is mostly in upper abdomen, burning in nature, improves after taking food, antacid but there is no radiation. She also complains of watery diarrhea but no mucus or blood. About 2 months back, she had fracture of her right arm following fall from standing height. For the last 1 month, she is complaining of repeated dizzy spells after prolonged fast, during exercise or on awakening from sleep. It improves after taking food in every time. There is no history of weight loss, fever, chest pain. She was treated with omeprazole, antacid and vitamins. There is no history of such illness in her family.

My diagnosis is MEN-1 (components are primary hyperparathyroidism, Gastrinoma, Insulinoma).

Q. What are your **differential diagnoses?**

A. As follows:

- Diabetes Mellitus with PUD
- Sporadic primary hyperparathyroidism
- Multiple myeloma.

Q. What **investigations** would you do?

A. As follows:

- Serum calcium, phosphate
- Serum albumin
- Serum PTH, gastrin, prolactin, GH, ACTH
- Ultrasonogram of neck
- Sestamibi scan of parathyroid gland
- Plain X-ray abdomen
- Endoscopic ultrasound, CT abdomen, octreotide scanning
- Fasting Insulin and Glucose, endoscopic ultrasound, CT/MRI abdomen
- X-ray skull, MRI of pituitary gland.

Q. What is the **treatment** of MEN-I?

A. As follows:

1. Therapy for MEN-1 includes surgical resection of hyperplastic parathyroid tissue and pituitary adenomas; surgical cure for the associated pancreatic tumor is usually not possible.
2. For gastrinoma proton pump inhibitor is the mainstay of treatment.
3. Surgery is the treatment of choice in case of insulinoma and non surgical candidate can be managed with diazoxide or verapamil.

CASE 2

Chief Complaints

- Pain in the epigastrium for … months.
- Anorexia, nausea and constipation for … months.
- Recurrent attack of headache, sweating, insomnia and palpitation for … months.

History of present illness: The patient states that she was well about … months back. Since then, she has been suffering from pain in the epigastrium, which is burning in nature, sometimes relieved

by taking food, but no radiation. She also complains of anorexia, nausea and occasional vomiting for … months. The patient is experiencing recurrent attack of headache, sweating, insomnia and palpitation for the last … months. There is no history of weight loss, fever, chest pain.

Other history: Mention accordingly.

Examination: BP 185/120 mm Hg, pulse 110/min. A small goiter, irregular, nodular, non-tender and hard in consistency, no bruit.

Salient feature: Mention as above.
My diagnosis is MEN-IIa.

Q. Why MEN-IIa?

A. In this patients there is goiter (may be medullary carcinoma of thyroid), features of pheochromocytoma (hypertension, recurrent headache, sweating) and hypercalcemia (anorexia, nausea, constipation – may be hyperparathyroidism).

Q. What **investigation** should be done in MEN-2a?

A. As follows:
- For hyperparathyroidism – serum calcium (high), phosphate (low), alkaline phosphatase (high).
- For pheochromocytoma – serum catecholamine (high), 24 hours urinary VMA (high).
- For MTC – serum calcitonin (high).
- Other investigations – accordingly.

RELATED QUESTIONS AND ANSWERS

Q. What is **MEN**?

A. MEN is a group of genetic syndromes, transmitted as autosomal dominant manner characterized by neoplasm of two or more different hormonal tissue of the body. It is a common and mostly in **4th and 5th** decades.

Q. What **other features** you would search for in this case?

A. Presence of galactorrhea as pituitary adenoma, mostly prolactin secreting, is an important component of MEN-1

Q. What are the types of MEN?

A. Two types:

MEN-1 (Wermer's syndrome): It comprises primary hyperparathyroidism, pituitary adenoma and pancreatic tumor.
- Primary hyperparathyroidism—most common feature and earliest manifestation of MEN-1. There are four gland hyperplasia.
- Pancreatic neuriendocrine tumor—gastrinoma (40% to 60%), insulinoma (20%).
- Pituitary adenomas—the majority secrete prolactin.

MEN-2a (Sipple's syndrome): It comprises:
- Medullary carcinoma of thyroid
- Primary hyperparathyroidism (usually hyperpalasia)
- Pheochromocytoma.

MEN-2b: MEN-2a when associated with:
- Marfanoid body habitus
- Abnormal dental enamel

- Multiple mucosal neuromas
- Skeletal abnormalities.

Q. Is hyperparathyroidism in **MEN-1** is similar to sporadic hyperparathyroidism?

A. No. Hyperparathyroidism associated with MEN-1 results from hyperplasia of all four glands, whereas sporadic primary hyperparathyroidism is usually characterized by adenoma in a single gland.

Q. What **other pancreatic tumors** may be seen in MEN-1?

A. Glucagonoma, somatostatinoma, VIPomas.

Q. At what age screening for **MEN-1** should begin?

A. Screening should not begin before the age of 15 and may be unnecessary for people after the age of 50, who are disease free.

Q. What are the **treatments** of MEN-2?

A. Treatment for MEN-2 includes surgery for medullary carcinoma of thyroid and pheochromocytoma.

CHAPTER 10

Hematology

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CHRONIC MYELOID LEUKEMIA

CHIEF COMPLAINTS

- Weakness and dizziness for … months
- Feeling of a lump in the left upper abdomen for … months
- Anorexia, weight loss, palpitation for … months
- Occasional gum bleeding for … months.

HISTORY

History present illness: The patient states that he was alright … months back. Since then, he has been suffering from severe weakness with occasional dizziness. He finds it difficult to perform regular daily activities. The patient also feels a lump in the left upper abdomen which is associated with heaviness and occasional dull pain for … months. He also complains of loss of appetite, loss of about 20 kg of body weight, palpitation and occasional gum bleeding for … months. There is no history of fever, bowel or bladder abnormality or other bleeding manifestations.

History of past illness

Family history

Personal history

Socioeconomic history

Drug history: Mention according to the patient's statement

GENERAL EXAMINATION

- The patient looks pale and emaciated
- Moderately anemic
- No jaundice, clubbing, cyanosis, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- There is sternal tenderness
- Pulse: 80/min
- BP: 130/85 mm Hg
- Temperature: 97ºF.

SYSTEMIC EXAMINATION

Gastrointestinal System

- Lips, gums, teeth and tonsils—normal
- Tongue and oral cavity—pale.

Abdomen

Inspection:

- Distension in upper abdomen, more marked in left upper quadrant.

Palpation:

- Liver—just palpable, 2 cm from the right costal margin in the midclavicular line, margin is sharp, surface is smooth, nontender and firm in consistency, no bruit or rub.
- Spleen—hugely enlarged, 15 cm from the left costal margin in the anterior axillary line towards the right iliac fossa.
- Kidneys—not ballotable.

Percussion:

- No evidence of ascites (no fluid thrill, no shifting dullness).

Auscultation:

- No abnormality detected.

Cardiovascular System

- There is a systolic murmur in the apical area (likely to be flow murmur).

Examination of other systems reveals no abnormalities.

SALIENT FEATURE

Mr …, 42 years old, government service holder, normotensive, nondiabetic, nonsmoker, hailing from …, presented with severe weakness with occasional dizziness for … months. He finds it difficult to perform regular daily activities. The patient also feels a lump in the left upper abdomen which is associated with heaviness and occasional dull pain for … months. He also complains of loss of appetite, loss of about 20 kg of body weight, palpitation and occasional gum bleeding for … months. There is no history of fever, bowel or bladder abnormality or other bleeding manifestations. He was treated with ranitidin, iron tablets and vitamins. There is no such illness in his family.

On examination—general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is hepatosplenomegaly with severe anemia for which I have some differential diagnoses:

- Chronic myeloid leukemia
- Chronic liver disease with portal hypertension
- Myelofibrosis
- Tropical splenomegaly syndrome.

Q. What are the causes of **massive splenomegaly?**

A. As follows:

- Chronic myeloid leukemia
- Kala-azar
- Malaria
- β thalassemia major
- Myelofibrosis
- Gaucher's disease
- Hairy cell leukemia.

Q. Mention **one single investigation** which will help in diagnosis or exclude other diagnosis.

A. Full blood count with PBF. It will help:

- To diagnose CML.
- Myelofibrosis (it will show leukoerythroblastic blood picture with tear or pear drop poikilocytes).
- Pancytopenia (due to hypersplenism).

Q. What **investigations** do you suggest in CML?

A. As follows:

1. FBC. It shows:
   - Leukocytosis (may be very high)
   - Differential count (DC) shows increase in myelocyte, promyelocyte. Metamyelocyte, myeloblast < 10%, increase in neutrophil, also basophil and eosinophil
   - Platelets are increased
   - Nucleated red cells are common.

2. Bone marrow study (hypercellular marrow with increase myeloid precursors). Cytogenetic analysis for Philadelphia chromosome, also RNA analysis to see the presence of BCR-ABL gene product.

3. Other tests:
   - Philadelphia chromosome (positive in 95% cases)
   - LAP score (decreases)
   - Serum uric acid (increases)
   - Serum vitamin B12 (increases)
   - Serum LDH (increases).

RELATED QUESTIONS AND ANSWERS

Q. What is the **CML**?

A. It is a myeloproliferative disorder, characterized by overproduction of myeloid cells and presence of Philadelphia chromosome. It is common in 40 to 60 years, and peak age is 55 years.

Q. What are the **myeloproliferative disorder**?

A. Group of disease consisting of:

- Chronic myelocytic leukemia
- Myelofibrosis
- Polycythemia rubra vera
- Essential thrombocythemia.

These disorders are grouped together, because any of the disease may evolve from one form to another. All myeloproliferative disorders may progress to acute myeloid leukemia.

Q. How does the patient usually **present**?

A. As follows:

- May be asymptomatic (25%)
- Splenomegaly (90%). In 10% cases, there may be huge splenomegaly. The Patient may complain of mass or discomfort or heaviness or pain in left hypochondrium. A friction rub may indicate splenic infarction
- Unexplained aneia
- General features—weakness, tiredness, lethargy, anorexia, loss of weight and night sweating
- Repeated infection

- Breathlessness
- Bleeding, bruising (due to thrombocytopenia)
- Hepatomegaly (in 50% cases).

Q. What are the **clinical phases or types** of CML?

A. Three phases:
- Chronic phase
- Accelerated phase
- Blastic crisis.

Q. What is **blastic** crisis? How can you **suspect** blastic crisis clinically in CML?

A. It means the disease is transformed to acute leukemia. It may be myeloid (70%) or lymphatic type (30%), and it occurs at a rate of 10% per year, relatively refractory to treatment and is the cause of death in majority of cases. Prognosis is poor in myeloid type of blastic crisis.

Blastic crisis in CML can be suspected, if:
- Rapid deterioration of the patient
- Increasing splenomegaly
- Blood picture shows increase in number of blast cells and increasing basophil.

Q. What are the **causes of death** in CML?

A. As follows:
- Blastic crisis
- Secondary infection
- Myelofibrosis.

Q. How to **treat** CML?

A. Treatment depends on the phase of the disease such as chronic phase and accelerated or blastic crisis:

1. Treatment of chronic phase:
- Imatinib is the first line therapy. It shows 76% (95% in some cases) response with disappearance of Ph chromosome after 18 months. It is a tyrosine kinase inhibitor, acts by blocking the enzymatic action of BCR-ABL fusion protein. It reduces uncontrolled proliferation of WBC. Dose is 400 mg daily. In some cases, 600 to 800 mg may be given to overcome the resistance. It can be continued indefinitely.
- If failure to respond to imatinib, second generation tyrosine kinase inhibitor such as desatinib or nilotinib or allogenic bone marrow transplantation should be considered.
- Alternately, hydroxyurea or α-interferon that were previously used for initial control, are still useful. However, hydroxyurea does not diminish Ph-chromosome or affect blastic crisis. α-interferon was given alone or with the chemotherapeutic agent Ara-C. It controls CML in chronic phase in about 70% of patients and causes disappearance of Philadelphia chromosome in 20% cases. It was a first line drug before imatinib.
- Busulphan was used previously. Not used now a days.
- Bone marrow transplantation (BMT) from allogenic matched sibling donor (usually below the age of 40 years and in early chronic phase), 70% cure.

2. Treatment of accelerated phase and blastic crisis:
- Treatment is difficult, imatinib is indicated if the patient has not received it.
- Hydroxyurea (hydroxycarbamide) can be effective.
- Low-dose cytarabine can be given.

Note Remember the following points regarding the previous chemotherapeutic drugs:

- Both busulphan and hydroxyurea—less or no use now
- Busulphan controls leukocyte quickly, but greater risk of marrow depression and rarely interstitial fibrosis of lung (**Busulphan lung**). Also increased pigmentation.
- Hydroxyurea is preferred than busulphan, but controls leukocyte count less quickly than busulphan and bone marrow depression is also less.
- None of these drugs affect the onset of blast transformation or diminishes Philadelphia chromosome and little effect on survival.
- Bone marrow transplantation is indicated in whom the disease is not well controlled, in whom the disease progress after initial control or for those who have accelerated phase disease.

Q. What are the therapies that may **cure** CML?

A. Bone marrow transplantation (BMT), imatinib and α-interferon.

Q. What is the **prognosis** of CML?

A. As follows:

- With imatinib therapy, complete hematological remission in up to 95% cases, and 70 to 80% of these have no detectable BCR-ABL transcript. Event free and overall survival appear to be better
- Following stem cell transplantation, there is 70% cure in chronic phase in young patients
- Without treatment median survival is 3 to 4 years, some may survive up to 10 years
- If there is blastic crisis, prognosis is poor. Median survival is 6 months
- CML may transform to myelofibrosis.

CHRONIC LYMPHATIC LEUKEMIA

CHIEF COMPLAINTS

- Weakness for … months
- Occasional fever with cough for … months
- Lumps in the neck and inguinal region for … days.

HISTORY

History of present illness: The patient states that he was alright … months back. Since then, he has been suffering from severe generalized weakness, which interferes with his day to day activities. He also complains of occasional fever and cough for … months. Fever is usually low grade, not associated with chills and rigor, no evening rise of temperature, does not subside with sweating. Cough is usually dry, not associated with difficulty in breathing or hemoptysis. For the last few days, the patient noticed painless lumps involving both sides of the neck and inguinal region, which are gradually increasing in size. There is no history of weight loss, bleeding from any site, polyarthritis, skin rash, contact with TB patients or history of exposure.

History of past illness

Family history

Personal history

Socioeconomic history

Drug history: Write according to the statement of the patient.

GENERAL EXAMINATION

- The patient is ill-looking and mildly anemic
- No jaundice, clubbing, cyanosis, koilonychia, leukonychia or edema
- No thyromegaly
- There are generalized lymphadenopathy involving cervical, axillary and inguinal lymph nodes of both sides. The lymph nodes are of variable size and shape, largest one being 2 × 2 cm, nontender, firm in consistency, discrete, not adherent to the underlying structure or to the overlying skin. There is no discharging sinus
- Pulse: 80/min
- BP: 130/85 mm Hg
- Temperature: 98ºF
- Respiratory rate: 18/min.

SYSTEMIC EXAMINATION

Gastrointestinal System

- Lips, gums, teeth, tongue, oral cavity and tonsils—normal.

Abdomen

Inspection:

- No abnormality detected.

Palpation:

- Liver—just palpable, 1 cm from the right costal margin in the midclavicular line, margin is sharp, surface is smooth, nontender and firm in consistency, no hepatic bruit or rub.
- Spleen—just palpable, 2 cm from the left costal margin in the anterior axillary line towards the right iliac fossa.
- Kidneys—not ballotable.

Percussion:

- No evidence of ascites (no fluid thrill, no shifting dullness).

Auscultation:

- No abnormality detected.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr. …, 28 years old, businessman, normotensive, nondiabetic, nonsmoker, hailing from …, presented with severe generalized weakness for … months, which interferes with his day to day activities. He also complains of occasional fever and cough for … months. Fever is usually low grade, not associated with chills and rigor. Cough is usually dry, not associated with difficulty in breathing or hemoptysis. For the last few days, the patient noticed painless lumps involving both sides of the neck and inguinal region, which are gradually increasing in size. There is no history of weight loss, bleeding from any site, polyarthritis, skin rash, contact with TB patients or history of exposure. He was treated with paracetamol and several antibiotics, the name of which he cannot mention. There is no family history of such illness.

On examination—general examination (mention as above, describe specially the lymph nodes).

Systemic examination—hepatosplenomegaly (mention as above).

Examination of other systems reveals no abnormalities.

Provisional diagnosis—With this history and clinical findings of lymphadenopathy and hepatosplenomegaly, I have some differential diagnoses:

- Chronic lymphatic leukemia
- Lymphoma
- Acute lymphoblastic leukemia
- Disseminated tuberculosis.

Q. What **investigations** do you suggest in CLL?

A. As follows:

1. CBC, showsL
   - Hb% (low)
   - Leukocytosis (50 to 200 × 10^9/L)
   - Differential count (DC) shows increased lymphocytes (95%), mostly small lymphocytes
   - Platelet is normal, low or slightly increased.

2. Bone marrow (increased lymphocytes).

3. Others:
   - Reticulocyte (high in autoimmune hemolytic anemia)
   - Coombs' test (positive in autoimmune hemolytic anemia)
   - Paraproteins (may be increased)
   - Uric acid (high)
   - Immunophenotyping of B-cell antigen (CD19 and CD23) and T-cell antigen (CD5).

RELATED QUESTIONS AND ANSWERS

Q. What is **chronic lymphatic leukemia?**

A. It is a neoplastic disorder of lymphocyte, usually involving the B lymphocytes (95%) and rarely T lymphocytes (5%). It is more in males than females (2:1), usually after 45 years.

Q. How does the patient of CLL usually **present**?

A. CLL is common in the elderly, 65 to 70 years. M:F = 2:1.

- Asymptomatic (25%), diagnosed incidentally in routine examination.
- General features like malaise, weakness, fatigue, weight loss and night sweating.
- Features of anemia (usually slowly developing anemia).
- Recurrent infections.
- Generalized lymphadenopathy (detected on routine examination).
- Hepatosplenomegaly (huge splenomegaly, if autoimmune hemolytic anemia).
- Bleeding manifestations—uncommon.

Q. Why there is **anemia** in CLL?

A. Anemia is due to bone marrow infiltration or autoimmune hemolytic anemia.

Q. What are the **stages** of CLL?

A. Three stages (**Binet staging**):

- Stage A (60%)—survival > 10 years.
  - No anemia
  - No thrombocytopenia
  - Less than 3 areas of lymph nodes involvement.
- Stage B (30%)—survival 7 years.
  - No anemia
  - No thrombocytopenia
  - 3 or more areas of lymph nodes involvement.
- Stage C (10%)—survival 2 years.
  - Anemia
  - With or without thrombocytopenia
  - Regardless of area of lymph nodes involvement.

Note Remember the following:

Lymphoid enlargements include cervical, axillary, inguinal and liver and spleen enlargement.

Another staging (**Rai staging**):

- **Stage 0:** Lymphocytosis (in blood and bone marrow) >15000/cmm, without lymphadenopathy, hepatosplenomegaly, anemia or thrombocytopenia
- **Stage I:** Lymphocytosis with lymphadenopathy (without hepatosplenomegaly, anemia or thrombocytopenia)

- **Stage II:** Lymphocytosis with hepatomegaly or splenomegaly (with or without lymphadenopathy)
- **Stage III:** Lymphocytosis with anemia (Hb% <11g/dL) with or without hepatomegaly or splenomegaly
- **Stage IV:** Lymphocytosis with thrombocytopenia (<100000/cmm) with or without lymphadenopathy, hepatomegaly, splenomegaly or anemia.

Q. How to **treat** CLL?

A. Many early indolent cases of CLL require no treatment, even in 30% case will never require any intervention. Otherwise, treatment depends on stage of disease:

- Stage A—No treatment, unless progression occurs. The patient survives for long time (reassurance and follow up). Life expectancy is normal in older patients
- Stage B—No treatment, if the patient is asymptomatic
- Stage C—Usually treatment is necessary.

Indications of treatment in CLL:

- Evidence of marrow failure indicated by worsening of anemia or thrombocytopenia
- Massive or progressive lymphadenopathy or splenomegaly
- Doubling of lymphocyte count in 6 months
- Symptoms (fever, night sweating and weight loss)
- Presence of hemolysis or other immune mediated cytopenias
- Recurrent infection.

Mode of treatment:

1. Symptomatic:
   - For anemia and thrombocytopenia—prednisolone, blood transfusion should be given. If it is refractory or recurrent, then splenectomy may be done, which is also indicated for hypersplenism
   - Infection—antibiotic, immunoglobulin (gamma globulin 0.4 g/kg/month)
   - Local radiotherapy for LN causing discomfort or local obstruction and symptomatic splenomegaly.
2. Specific:
   - Chlorambucil 5 mg daily, adjust the dose according to blood count.
   - Fludarabine alone or with cyclophosphamide or mitoxantrone (with or without steroid) is very helpful. Fludarabine should be avoided in autoimmune hemolytic anemia as it aggravates anemia.
   - Combination therapy with rituximab plus fludarabine with or without cyclophosphamide is the treatment of choice. Rituximab alone is ineffective.
   - Alemtuzumab may be used in patient that progress after fludarabine.
   - Allogenic stem cell transplantation may be curative, but only used in those patient whose disease cannot be controlled by standard therapies.

Q. What is the **prognosis** of CLL?

A. As follows:

- Median survival is about 6 years
- Stage A may be normal life expectancy
- In stage C, median survival is 2 to 3 years
- About 50% dies from infection and 30% from causes unrelated to CLL
- Rarely, acute blastic crisis may occur.

Q. What is **Richter's syndrome?**

A. When CLL is transformed to aggressive high-grade lymphoma, it is called Richter's syndrome. Its prognosis is poor with median survival less than 1 year.

LYMPHOMA

CHIEF COMPLAINTS

- Fever with cough for … months
- Weakness, loss of weight, loss of appetite for … months
- Lumps in the neck and inguinal region for … days.

HISTORY

History of present illness: The patient states that he was alright … months back. Since then, he has been suffering from occasional fever which is low grade, continued, not associated with chill and rigor. There is occasional evening rise of temperature and night sweating. He also complains of cough which is dry, worse at night, associated with difficulty in breathing and more marked on moderate to severe exertion. There is no history of orthopnea or paroxysmal nocturnal dyspnea. The patient also complains of severe weakness, marked loss of weight and appetite for … months. For the last … days, he noticed painless lumps initially on the right side of his neck, and then on the axilla and groins. These lumps are gradually increasing in size. There is no history of bleeding from any site, polyarthritis, skin rash, contact with TB patients or history of exposure. His bowel and bladder habits are normal.

History of past illness

Family history

Personal history

Socioeconomic history

Drug history: Mention according to the statement of the patient.

GENERAL EXAMINATION

- The patient is cachexic and moderately anemic
- No jaundice, clubbing, cyanosis, koilonychia, leukonychia or edema
- Thyromegaly absent
- There is generalized lymphadenopathy involving right cervical, both axillary and inguinal region. The lymph nodes are of variable size and shape, largest one being 2 × 2 cm, nontender, firm in consistency, discrete, not adherent to the underlying structure or to the overlying skin. There is no discharging sinus
- There is no sternal tenderness
- Pulse: 100/min
- BP**:** 100/85 mm Hg.

SYSTEMIC EXAMINATION

Gastrointestinal System

- Lips, gums, teeth, oral cavity and tonsils—normal
- Tongue—pale and smooth.

Abdomen

Inspection:

- No abnormality detected.

Palpation:

- Liver—palpable, 4 cm from the right costal margin in the midclavicular line, margin is sharp, surface is smooth, nontender and firm in consistency, no hepatic bruit or rub.
- Spleen—palpable, 10 cm, from the left costal margin in the anterior axillary line towards the right iliac fossa.

Percussion:

- No evidence of ascites (no fluid thrill, no shifting dullness).

Auscultation:

- No abnormality detected.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 38 years old, fisherman, normotensive, nondiabetic, nonsmoker, hailing from …, presented with occasional fever for … months that is low grade, not associated with chill and rigor. There is occasional evening rise of temperature and night sweating. He also complains of cough which is dry, worse at night, associated with difficulty in breathing and more marked on moderate to severe exertion. There is no history of orthopnea or paroxysmal nocturnal dyspnea. The patient also complains of severe weakness, marked loss of weight and appetite for … months. For the last … days, he noticed painless lumps initially on the right side of his neck, and then on the axilla and groins. These lumps are gradually increasing in size. There is no history of bleeding from any site, polyarthritis, skin rash, contact with TB patients or history of exposure. His bowel and bladder habits are normal. There is no family history of such illness. He has been treated with paracetamol, cough syrup, salbutamol and various antibiotics the name of which he could not mention.

On examination—general examination (mention as above).

Systemic examination (mention as above).

Provisional diagnosis: With this history of fever, lymphadenopathy and hepatosplenomegaly, I have some differential diagnoses:

- Lymphoma
- Disseminated tuberculosis
- Sarcoidosis
- Chronic lymphatic leukemia
- SLE.

Q. What are the causes of **generalized lymphadenopathy?**

A. As follows:

1. Hematological malignancy—lymphoma, ALL, CLL
2. Viral fever—infectious mononucleosis, CMV infection, HIV
3. Disseminated tuberculosis, brucellosis, toxoplasmosis
4. Sarcoidosis

5. SLE
6. Drugs—phenytoin or diphenylhydantoin (called pseudolymphoma).

Q. Could it be **kala-azar?**

A. It could be kala-azar, because of long term fever and hepatosplenomegaly. But lymphadenopathy is not common in kala-azar (However it is common in African and Chinese kala-azar).

Q. What **investigations** do you suggest for this patient?

A. As follows:

1. Full blood count with PBF examination
2. X-ray chest
3. USG of whole abdomen
4. Urine R/E
5. Others according to the suspicion of cause:
   - If lymphoma is suspected—FNAC or biopsy (biopsy is preferable) of lymph nodes
   - If leukemia is suspected—bone marrow study
   - If disseminated tuberculosis—MT, lymph node FNAC or biopsy
   - If SLE—ANA, anti-ds-DNA, etc.

RELATED QUESTIONS AND ANSWERS (LYMPHOMA)

Q. What is **lymphoma**?

A. Lymphoma is a group of disorders due to neoplastic proliferation of lymphoid tissue. Majority are B cell origin. There are 2 types:

- Hodgkin's disease (HD).
- Non-Hodgkin's lymphoma (NHL).

Q. What is **Hodgkin's disease**?

A. It is a type of lymphoma characterized by painless, progressive enlargement of lymph nodes associated with **Reed Sternberg giant cell** (hallmark of the disease). It usually occurs in adolescence and young adults (20 to 35 years of age), also after 45 years of age (50 to 70 years, two peaks of incidence). Median age is 31 year. More in males than females (1.5:1). It is three times more with past history of infectious mononucleosis.

Q. What is **Reed–Sternberg cell**?

A. It is a malignant cell of B-cell origin, characterized by:

- Large cell with paired mirror image nuclei that resembles "Owl's eye" appearance.
- Prominent nucleoli.

Reed-Sternberg cell is the hallmark of Hodgkin's disease. Rarely, found in infectious mononucleosis, recurrent Burkitt's lymphoma and CLL.

Q. What are the **types** of Hodgkin's disease?

A. There are two types of Hodgkin's disease:

1. Nodular lymphocyte predominant Hodgkin's lymphoma (HL)—5%, slowly growing, localized and rarely fatal.

2. Classical HL, which is of 4 types:
   - Nodular sclerosing (70%, common in young, female. Mainly involves cervical, supraclavicular and mediastinal lymph node.)
   - Mixed cellularity (20%, common in elderly, men, associated with B symptoms)

- Lymphocyte rich (5%, common in men, characterized by an infiltrate of many small lymphocytes and Reed-Sternberg cells. It often involves the peripheral lymph nodes. It is usually an indolent disease, which presents at a higher median age)
- Lymphocyte depleted (rare, probably represents large cell or anaplastic NHL. There is lack of cellular infiltrate with numerous Reed-Sternberg cells. It typically presents with advanced stage and B symptoms. It is seen in Hodgkin's disease associated with HIV).

Q. How does the patient **present** in Hodgkin's disease?

A. As follows:

- May be asymptomatic
- The patient may present with generalized lymphadenopathy starting in cervical glands, then axillary and inguinal. These are painless, discrete and rubbery. Pattern of spread is contiguous
- Dry cough, shortness of breath (due to mediastinal lymphadenopathy)
- Systemic features—fever, drenching night sweat, loss of weight, malaise, weakness and pruritus (10%)
- Hepatosplenomegaly
- After alcohol intake, pain at the site of LN involvement.

Q. What is **Pel–Ebstein fever**?

A. Recurrent bouts of pyrexia followed by apyrexial period. May occur in 10% cases of HD.

Q. What are the **stages** of HD?

A. According to Ann-Arbor staging classification, there are is stages:

- Stage I—Involvement of a single LN region (I) or extralymphatic site (I_E).
- Stage II—Involvement of two or more LN regions (II) or an extralymphatic site and LN regions on the same side of diaphragm (II_E).
- Stage III—Involvement of LN regions on both sides of diaphragm with (III_E) or without (III) localized extralymphatic involvement or involvement of spleen (III_S) or both (III_{SE}).
- Stage IV—Diffuse involvement of one or more extralymphatic tissue with or without LN involvement (bone marrow, liver and lung).

(Lymphatic structures include LN, spleen, thymus, Waldeyer's ring, appendix and Peyer's patch.)

Depending on systemic features, each stage is divided into 2 phase:

- No systemic features.
- With systemic features (B symptoms)—such as fever (temperature > 38ºC), drenching sweats, unexplained loss of > 10% of body weight within the previous 6 months.

Q. What **investigations** are done in HD?

A. As follows:

1. CBC—may be normal. There may be normocytic normochromic anemia, lymphopenia, high eosinophil and high ESR.
2. Chest X-ray (shows bilateral hilar lymphadenopathy and widening of mediastinal shadow).
3. FNAC or biopsy—biopsy is preferable (to see the architecture of lymph node which may not be detected by FNAC, also biopsy is necessary for staging).
4. USG of whole abdomen.
5. CT scan of chest and abdomen including pelvis (necessary for staging).
6. Others:
   - PET (Positron emission tomography)—used for staging, assessment of response and direction of therapy.
   - Bone marrow study (involved in advanced stage).

- Renal function tests—mainly creatinine (necessary prior to treatment).
- Liver function tests—mainly SGPT (necessary prior to treatment)
- Serum uric acid (necessary prior to treatment).
- Serum lactate dehydrogenase (LDH).

Note Remember the following points:

- Lymphopenia, high LDH and lymph node > 10 cm are poor prognostic factors
- High ESR is an indicator of disease activity
- High alkaline phosphatase (biliary obstruction) indicates involvement of lymph nodes in porta hepatis.

Q. How is **staging** done and why?

A. For staging, following tests are done:

- Chest X-ray
- Bone marrow
- USG of whole abdomen
- CT scan (whole abdomen and chest).

Staging is done for selection of therapy (radiotherapy or chemotherapy) and prognosis.

Q. How to **treat** HD?

A. As follows:

1. Majority of HD patients are now treated with chemotherapy and adjunctive radiotherapy. ABVD (Adriamycin or doxorubicin, Bleomycin, Vinblastine and Dacarbazine) regimen is widely used. ABVD chemotherapy can cause cardiac and pulmonary toxicity, due to doxorubicin and bleomycin respectively. Infertility and secondary myelodysplasia or AML is low with this regime.
2. Patient with early stage HD (IA, IIA, no bulk) is treated with 2 to 4 cycles of ABVD followed by radiotherapy (20 to 30 Gy) to the involved lymph nodes. Treatment response is monitored by CT scan or PET scan.
3. Patient with advanced disease is usually treated with chemotherapy alone. Usually 6 to 8 cycles of ABVD is given. Radiotherapy at the bulk site used previously is now avoided. Achieving PET negative remission predicts a better long term remission rate. Overall, the long term disease control or cure rates are lower with advanced disease.
4. New regimens are being tested for those who fail with above therapy (about 25%). This includes BEACOPP (Bleomycin, Etoposide, Adriamycin or doxorubicin, Cyclophosphamide, Oncovin or vincristine, Procarbazine, Prednisolone).
5. Patient who is resistant to chemotherapy may be considered for autologous bone marrow transplantation.

Other chemotherapeutic regimen that were previously used are as follows:

- MOPP—Mechlorethamine, Oncovin (vincristine), Procarbazine and Prednisolone.
- COPP—Cyclophosphamide, Oncovin (vincristine), Procarbazine and Prednisolone.

Q. What is the **prognosis** of HD?

A. Prognosis depends on the stage:

- Early stage HD—complete remission in > 90%, when treated with chemotherapy followed by radiotherapy. The majority are cured.
- Advanced stage HD—50 to 70% can be cured.
- Patients who fail to respond to initial chemotherapy have a poor prognosis, but some may achieve long term survival after autologous bone marrow transplantation.

- Patients relapsing within a year of initial chemotherapy have a good salvage rate with autologous BMT.
- Patients relapsing after 1 year may obtain long term survival with further chemotherapy alone.
- Presence of B symptoms indicate adverse prognosis.

Note Remember the following points:

- Fertility is usually preserved after radiotherapy.
- In young women with mediastinal disease, radiotherapy to the breast may cause breast cancer (hence, needs follow up).
- Patients who continue to smoke after chest radiotherapy, lung cancer may occur.
- Cardiac disease may occur after supradiaphragmatic mantle field radiation.

Q. What is **disease free** or **cure** in HD?

A. If no relapse after 5 years of withdrawal of treatment, it is called cure or disease-free.

BRIEF DISCUSSION ABOUT NON-HODGKIN'S LYMPHOMA

Q. What is **non-Hodgkin's lymphoma (NHL)**? What are the **types (grading)**?

A. The NHL is characterized by malignant proliferation of lymphoid cells, and majority are B-cells (70%) and few T-cells (30%).

Types or grading (depending on the rate at which the cells are dividing):

1. **Low grade (indolent)** shows the following characteristics:
   - Low cell proliferation rate
   - Asymptomatic for many years
   - Slow indolent course
   - Remitting and relapsing course
   - Good response to minimal therapy
   - Incurable, but the patient survives for long time
   - Most nodular lymphoma are of low grade
   - Small cell disease (mature lymphocyte) is associated with low-grade lymphoma
   - No treatment is required, if the disease is not advanced and asymptomatic
   - Median survival up to 10 years
   - Transformation to high grade is associated with poor prognosis.
2. **High grade (aggressive)** shows the following characteristics:
   - Cell divisions occur quickly
   - Early symptoms are common
   - Fatal, if untreated
   - Responds better to treatment and patient may achieve a long-term remission, if treated properly (potentially a curable disease)
   - 80% respond to initial therapy, and 35% are disease free for 5 years
   - Large cell disease (immature lymphoid cells) is of high grade
   - Most diffuse lymphomas are of high grade.

Note Remember the following:

Stages of NHL are similar to Hodgkin's lymphoma (HL).

Q. What are the **causes** of NHL?

A. Actual cause is unknown. Probable causes are:

- Specific lymphoma types are associated with EBV, human herpes virus 8 (HHV8) and human T-cell lymphotropic virus (HTLV) infection.
- *Helicobacter pylori* is an etiological factor in gastric MALT lymphoma.
- A late manifestation of HIV infection. Primary brain lymphoma, immunoblastic diffuse large B-cell lymphoma and Burkitt's lymphoma may occur in AIDS.
- Lymphoma occurs in congenital and acquired immunodeficiency states. Acquired immunodeficiency, as a result of organ transplantation, is strongly associated with NHL. These are commonly extranodal and most frequently occur in the first year after transplantation.
- Gastric lymphomas are associated with specific chromosome lesions. The t(14:18) translocation in follicular lymphoma results in the dysregulated expression of the BCL-2 gene product, which inhibits apoptotic cell death.
- A number of familial cancer syndromes are also associated with NHL.
- In autoimmune disorders, high risk of NHL is reported, e.g. Sjogren's syndrome, and extranodal marginal zone lymphoma.
- There may be an association with exposure to pesticide, hair dyes, organic solvents, etc.

Q. What are the **clinical features of NHL**?

A. As follows:

- NHL can occur at any age, but peak incidence is 65 to 70 years.
- It is multicentric in origin and spreads rapidly to noncontiguous areas. The disease is usually widespread at the time of diagnosis.
- Discrete, painless, firm, lymph nodal enlargement is the most common presentation. Waldeyer's ring and epitrochlear lymph nodes are frequently involved.
- B symptoms of fever, night sweats and weight loss are less prominent.
- Extranodal presentations are more common than Hodgkin's disease. May involve gastrointestinal tract (stomach), lung, thyroid, skin, testes and CNS. Skin involvement (T-cell lymphoma) presents as mycosis fungoides and Sezary syndrome. Oropharyngeal involvement occurs rarely. Compression syndrome may occur, such as paraplegia due to compression of spinal cord by an extradural lymphoma, dysphagia, breathlessness, vomiting, intestinal obstruction, ascites and limb edema, SVC obstruction.
- Bone marrow involvement is more common in low grade (60%) and less in high grade (10%).
- Involvement of liver and spleen results in hepatosplenomegaly.
- Bone involvement may manifest as pathological fractures with pain.

Q. What **investigations** are done in NHL?

A. Similar to HL, plus the following:

- Routine bone marrow aspiration and trephine.
- Immunotyping of surface antigen to distinguish T-cell and B-cell tumors (done on blood, marrow or nodal material). CD 20 should be done.
- Immunoglobulin determination (IgG or IgM paraprotein, which serve as markers for treatment response).
- Uric acid.

Q. What are the **treatment** of NHL?

A. As follows:

1. **Low-grade NHL—**Not cured by any therapy. No therapy, if the patient is asymptomatic. Indications of treatment are:
   - Marked systemic symptoms.
   - Bone marrow failure.
   - Features of compression (superior vena caval obstruction, spinal cord, gut obstruction and ascites).
   - Large lymphadenopathy causing discomfort or disfigurement.

   Treatment options include:
   - Radiotherapy, for stage I.
   - Chemotherapy is needed in most cases. Majority responds well to oral chlorambucil, which is well tolerated but not curative. More aggressive intravenous chemotherapy may be tried in younger age to provide better quality of life, but no survival benefit.
   - Monoclonal antibody—rituximab (anti-CD 20 antibody) is effective in 60% cases. Synergistic effects are seen with standard chemotherapy. Rituximab in combination with cyclophosphamide, vincristine and prednisolone (R-CVP) is recommended as first line therapy.
   - High dose chemotherapy and bone marrow transplantation can be tried in patient with relapse.
2. **High-grade NHL—**always needs treatment. Options are:
   - Majority (>90%) are treated with combination chemotherapy—CHOP (Cyclophosphamide, Hydroxydaunorubicin, Oncovin (vincristine) and Prednisolone).
   - Radiotherapy may be given in stage I. It is also indicated for the residual localized site of bulk disease after chemotherapy, for spinal cord and other compression syndrome.
   - Rituximab may be combined with CHOP therapy (R-CHOP). This helps in complete response rates and improves overall survival. It is the current first line therapy for those with stage II or greater diffuse large cell lymphoma.
   - Autologous bone marrow transplantation for relapse chemosensitive disease.

Q. What is the **prognosis?**

A. As follows:

1. Low grade lymphoma has a slow indolent course. Median survival up to 10 years. Transformation to high grade is associated with poor prognosis.
2. In high grade lymphoma, 80% respond to initial therapy, and 35% are disease free for 5 years.
3. Adverse prognostic factors in NHL includes:
   - Age > 60 years
   - Stage III or IV (advanced disease)
   - High serum LDH level
   - Performance status ECOG 2 or more
   - More than 1 extranodal site of involvement.
4. In case of high grade NHL, 5 year survival of patient with adverse prognostic factors (high risk score) is 25%, while that of patients without adverse prognostic factors (low risk score) is 75%.
5. Relapse is associated with a poor response to further chemotherapy (<10% 5-year survival), but in patients under 65 years, bone marrow transplantation improves survival.

Q. What is **Waldeyer's ring**?

A. It is a circle of lymphatic tissue in posterior part of oropharynx and nasopharynx, which includes tonsils and adenoids. It is involved in NHL, and rarely in HL.

Q. What are the **differences** between HL and NHL?

A. As follows:

Features	Hodgkin's lymphoma	Non-Hodgkin's lymphoma
1. Age	Bimodal. First peak at 20 to 30 years, and second peak at 50 to 70 years	Median age 65 to 70 years
2. LN involvement	Unifocal, usually localized to a single axial group (cervical and mediastinal)	Multicentric, more frequent involvement of peripheral LN
3. Mesenteric LN and Waldeyer's ring	Rarely involved	Commonly involved
4. Epitrochlear lymph node	Rarely involved	Commonly involved
5. LN spread	Orderly spread by contiguity	Noncontiguous spread (via blood)
6. Extranodal involvement	Less common, occurs late	More common, occurs early
7. Systemic features or B symptoms	Common	Less common
8. Alcohol induced discomfort at lymph node site	Present	Absent
9. Pel-Ebstein fever	May occur	Does not occur
10. Pruritus	Common	Less common
11. Histology	Reed-Sternberg cells (hallmark)	Absent
12. Bone marrow involvement	Early	Late
13. Prognosis	High cure rate	Low cure rate (low grade tumors are incurable)

APLASTIC ANEMIA

CHIEF COMPLAINTS

- Severe weakness, palpitation, dizziness for … months
- Occasional gum bleeding and nasal bleeding for … months
- Multiple bleeding spots in different parts of the body for … months
- Occasional fever and sore throat for … months.

HISTORY

History present illness: The patient states that he was alright … months back. Since then, he has been suffering from severe weakness, palpitation and dizziness, which is more marked even on mild activity. He also complains of occasional spontaneous bleeding from gum and nose for the same duration. For the last … months, he also noticed multiple bleeding spots in skin of different parts of body including hands, legs, abdomen, etc. There is also history of occasional fever, which is of low grade and associated with sore throat. He does not give any history of taking drugs, or exposure to radiation or chemicals. His bowel and bladder habits are normal.

History of past illness—Nothing significant.

Family history—There is no family history of bleeding disorder (like hemophilia).

Personal history—He is a day labor working in village (note that occupations like worker in radiotherapy, radiology, dye industry, naphthalene, etc. is very important, mention if any).

Socioeconomic history—mention according to the statement of the patient.

Drug & Treatment history— He took some antibiotics for his recurrent sore throat. He received 4 units of blood transfusions in the last 2 months.

GENERAL EXAMINATION

- The patient is ill looking and pale, severely anemic
- No jaundice, clubbing, cyanosis, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- No sternal tenderness
- There are multiple purpuric spots, bruises and ecchymoses on the arms, legs and trunks. These are of variable size and shape, painless and does not blanch on pressure
- Pulse: 110/min
- BP: 100/65 mm Hg.

SYSTEMIC EXAMINATION

Gastrointestinal System

- Lips, mouth, oral cavity—marked pallor
- Tongue—pale, smooth, shiny in appearance.

Abdomen

Inspection:

- Multiple purpuric spots and bruises are present. No organomegaly.

Palpation:

- Liver—not enlarged
- Spleen—not enlarged
- Kidneys—not ballotable.

Percussion:

- No evidence of ascites (no fluid thrill, no shifting dullness).

Auscultation:

- No abnormality detected.

Cardiovascular System

- There is a systolic murmur in the apical area (likely to be flow murmur).

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 31 years old, a day laborer, normotensive, nondiabetic, nonsmoker, hailing from …, presented with severe weakness, palpitation and dizziness for … months, which is more marked even on mild activity. He also complains of occasional spontaneous bleeding from gum and nose for the same duration. For the last … months, he also noticed multiple bleeding spots in skin of different parts of body including hands, legs, abdomen, etc. There is also history of occasional fever, which is of low grade and associated with sore throat. He does not give any history of taking drugs, or exposure to radiation or chemicals. His bowel and bladder habits are normal. There is no family history of bleeding disorder like hemophilia. He took some antibiotics for his recurrent sore throat. He received 4 units of blood transfusions in the last 2 months. There is no family history of similar illness.

On examination—general examination (mention as above).

Systemic examination (mention as above).

With this history and findings like severe anemia, multiple purpuric spots and ecchymoses, I have some **differential diagnoses**:

- Aplastic anemia
- Acute leukemia
- Idiopathic thrombocytopenic purpura.

Q. What **single investigation** do you suggest in this patient?

A. Full blood count with platelet and PBF. It shows the following:

- In aplasia—there will be pancytopenia.
- In acute leukemia—there may be leukocytosis with immature WBC (blast cells).
- In ITP—there will be thrombocytopenia.

Q. What **next** investigation do you suggest?

A. Bone marrow investigation. It shows following:

- In aplasia—either dry tap or markedly acellular or hypocellular marrow
- In acute leukemia—hypercellular with increased immature cells of WBC series
- ITP—increased megakaryocytes.

Q. What **investigations** do you suggest for aplastic anemia?

A. As follows:

- Full blood count—Pancytopenia (anemia, leukopenia and thrombocytopenia). Anemia is usually normocytic normochromic.
- Bone marrow study (aspiration and trephine biopsy)—either dry tap or markedly acellular or hypocellular marrow.

Q. What is **severe** aplastic anemia?

A. It is defined as:

- Neutrophil count < 500/cmm.
- Platelet < 20,000 / cmm.
- Reticulocyte < 1%.
- Bone marrow cellularity < 20%.

Q. What are the **causes** of aplastic anemia?

A. It may be primary or acquired.

1. Primary—may be congenital (Fanconi's anemia, Diamond-Blackfan anemia), may be idiopathic acquired (probably autoimmune).
2. Acquired or secondary. Causes are:
   - Drugs—cytotoxic drugs, antibiotics (chloramphenicol, sulfonamide), antithyroid drugs (carbimazole), carbamazepine, penicillamine.
   - Radiotherapy.
   - Chemicals—benzene, lindane, DDT.
   - Infection—viral hepatitis, EBV infection, HIV, parvoviral infection.
   - Miscellaneous—paroxysmal nocturnal hemoglubinurea, secondary deposits in bone marrow, lymphoma, multiple myeloma.

Q. What are the **presentations** of aplastic anemia?

A. As follows:

- Features of anemia—weakness, palpitation, dizziness or vertigo
- Bleeding manifestations
- Occasionally infection.

Note Remember the following:

On examination—Only physical findings are anemia and bleeding spots. No lymphadenopathy, hepatomegaly, splenomegaly or bony tenderness (which may be present in secondary deposit or secondary causes of aplastic anemia).

Q. What is the **treatment** of aplastic anemia?

A. As follows:

1. Removal of causative agent, if any.
2. Supportive therapy—blood transfusion, control of infection.
3. Allogenic bone marrow transplantation (with HLA matched siblings)—if the patient is below 30 years with severe idiopathic aplastic anemia. 75 to 90% long-term cure.

4. In older patient or if HLA matched donor is not available—immunosuppressive therapy with cyclosporine and anti thymocyte globulin (ATG) should be given. 5 years survival is about 75%. Tacrolimus may be used instead of cyclosporine. Steroids are used for serum sickness, due to ATG.
5. Other treatment—indicated if bone marrow transplantation is not possible:
   - Androgens (e.g. oxymetholone) are sometimes useful in patients not responding to immunosuppression and in patients with moderately severe aplastic anemia.
   - Prednisolone helpful in some cases specially congenital pure red cell aplasia (Diamond-Blackfan disease), also in adult with pure red cell aplasia. If associated with thymoma in adult pure red cell aplasia (30%), thymectomy may be done.

Q. What are the causes of **pancytopenia**?

A. As follows:

- Aplastic anemia
- Hypersplenism
- Megaloblastic anemia
- Banti's disease
- Aleukemic leukemia
- Some myelodysplastic syndrome
- Paroxysmal nocturnal hemoglobinuria
- Others—SLE, myelofibrosis, hairy cell leukemia, disseminated tuberculosis, leishmaniasis, brucellosis, HIV, multiple myeloma, lymphoma.

HEREDITARY HEMOLYTIC ANEMIA

CHIEF COMPLAINTS

- Severe weakness, palpitation, dizziness for … months
- Yellow discoloration of the eyes and high colored urine for … months
- Feeling of a mass in the left upper abdomen for … months
- Darkening of the skin color for … months.

HISTORY

History present illness: The patient states that he was alright … months back. Since then, he has been suffering from weakness, which is increasing day by day and now feels extremely tired even after mild activity. The patient also complains of palpitation with mild activity and dizziness on standing for … months. The patient also noticed yellow coloration of the eyes and high colored urine, which is not associated with pruritus or pale colored stool. There is no history of contact with a jaundice patient or any injection or infusion, but there is history of several units of blood transfusion every 4 to 6 months. The patient also states that he feels a mass in the left upper abdomen, which is progressively increasing in size and is not associated with pain but heaviness only. His skin is becoming dark, which is not associated joint pain, leg ulcer, hematemesis or melena.

History of past illness

Family history: One of his sisters is suffering from similar illness.

Personal history

Socioeconomic history: Mention according to the patient's statement

Drug and treatment history: He was hospitalized two times and received several units of blood transfusion during the last few years.

GENERAL EXAMINATION

- The patient is short for his age, pale and ill looking
- Face is mongoloid with prominent malar bones and supra orbital ridges, also frontal and parietal bossing
- Severely anemic, mildly icteric
- There is generalized pigmentation of skin
- No clubbing, cyanosis, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- No sternal tenderness
- Pulse: 120/min
- BP: 95/65 mm Hg.

SYSTEMIC EXAMINATION

Gastrointestinal System

- Lips, mouth, oral cavity—marked pallor, also looks yellow.
- Tongue—pale, smooth, shiny in appearance, also yellowish.

Abdomen

Inspection:

- Left upper abdomen is distended.

Palpation:

- Liver—enlarged, 10 cm from the right costal margin in the midclavicular line, surface is smooth, margin is sharp, nontender and firm in consistency, no hepatic bruit or rub.
- Spleen—hugely enlarged, 15 cm from the left costal margin in the anterior axillary line towards the right iliac fossa.
- Kidneys—not ballotable.

Percussion:

- No evidence of ascites (no fluid thrill, no shifting dullness).

Auscultation:

- No abnormality detected.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 18 years old, student, normotensive, nondiabetic, nonsmoker, hailing from …, presented with weakness for … months, which is increasing day by day and now he feels extremely tired even after mild activity. The patient also complains of palpitation with mild activity and dizziness on standing for … months. The patient also noticed yellow coloration of the eyes and high colored urine, which is not associated with pruritus or pale colored stool. There is no history of contact with a jaundice patient or any injection or infusion, but there is history of several units of blood transfusion every 4 to 6 months. The patient also states that he feels a mass in the left upper abdomen, which is progressively increasing in size and is not associated with pain but heaviness only. For his skin is becoming dark, which is not associated joint pain, leg ulcer, hematemesis or melena. One of his sisters is suffering from similar illness. He was hospitalized two times and received several units of blood transfusion during the last few years.

On examination—general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is hereditary hemolytic anemia, which may be:

- β-thalassemia major
- Hb E disease
- β-thalassemia Hb E disease (double heterozygous)
- Hereditary spherocytosis.

Q. What are your **differential diagnoses?**

A. As follows:

- Chronic liver disease with portal hypertension
- Lymphoma
- Kala-azar.

Q. Mention one **single investigation** which is helpful for your diagnosis.

A. Full blood count with PBF (which shows microcytic hypochromic blood picture).

Q. What **another hematological investigation** is helpful for your diagnosis?

A. Reticulocyte count (by supravital stain)—increased.

Q. How will you **confirm** your diagnosis?

A. Hemoglobin electrophoresis.

Q. What are the **findings** in Hb-electrophoresis in β-thalassemia?

A. As follows:

- β-Thalassemia major—Hb-F is high and Hb-A is less or absent.
- β-Thalassemia minor—Hb-A_2 is high.

Q. What are the causes of the **microcytic hypochromic blood picture**?

A. Causes are:

- Iron deficiency anemia—(commonest cause)
- β-thalassemia (major and minor)
- Sideroblastic anemia
- Anemia of chronic disease.

Q. What are the **diagnostic criteria** of hemolytic anemia?

A. **Triad** of:

- Anemia
- Jaundice
- Splenomagaly.

Q. What **investigations** should be done for hereditary hemolytic anemia?

A. As follows:

1. Hb%, TC, DC, ESR, PBF (microcytic hypochromic blood picture).
2. Reticulocyte count (by supravital stain)—increased.
3. Hemoglobin electrophoresis.
4. Others:
   - Serum bilirubin (also urinary urobilinogen will be high)
   - X-ray skull (also other skeletal survey)
   - X-ray chest
   - Serum iron profile (iron, TIBC, ferritin, % saturation).

RELATED QUESTIONS AND ANSWERS

Q. What is **thalassemia?**

A. It is an inherited disorder in which there is impairment of hemoglobin production due to partial or complete failure to synthesize the specific type of globin chain. It is of 2 types:

1. β-Thalassemia: In this case, there is an inadequate production of β-chain, causing less production of HbA. It is of 2 types.
   - β-Thalassemia major—HbA is less, HbF is more
   - β-Thalassemia minor—HbA_2 is increased.
2. α-Thalassemia: In this case, there is an inadequate production of α-chain, therefore less HbA, HbF and HbA_2, as all of them contain α-chain.

3. Thalassemia intermedia, characterized by the combination of homozygous mild β-thalassemia plus α-thalassemia. It is usually less severe and does not require blood transfusion, as anemia is mild to moderate.

Q. What are the **radiological findings** in skull in β-thalassemia major?

A. As follows:

- Widening of diploic space
- Thinning of outer table
- Thickening and coarsening of trabeculae giving rise to hair-on-end appearance.
- Sometimes, skull is enlarged with widening of suture.

Q. How to **treat** β-thalassemia major?

A. As follows:

1. Correction of anemia—Blood transfusion to keep Hb% above 10 g%, every 4 months (lifespan of RBC is 4 months).
2. Folic acid 5 mg daily, to be continued.
3. Iron containing drugs and diet are avoided (iron can only be given, if there is deficiency).
4. Repeated blood transfusion may cause hemosiderosis, which can be prevented by chelating agent, desferrioxamine subcutaneously with infusion pump overnight. Ascorbic acid 200 mg daily may be added (it causes urinary excretion of iron). Oral iron chelating agents such as deferiprone or deferasirox may be used.
5. Other treatment—
   - Injection erythropoietin. It stimulates the bone marrow, increases normal hemoglobin to some extent.
   - Hydroxyurea 1 to 2 g daily may be helpful (it prevents ineffective erythropoiesis).
6. Specific therapy—Allogenic bone marrow transplantation from HLA compatible sibling. Also, gene therapy.
7. Splenectomy.
8. Genetic counseling should be offered. It is necessary for prenatal diagnosis which is available.

Indication of splenectomy

- Huge splenomegaly with pressure symptoms
- Hypersplenism—as suggested by repeated transfusion in a short interval. Full blood count shows pancytopenia.

Note Remember the following:

In patient with mild thalassemia (β-thalassemia minor or α-thalassemia trait) requires no treatment. Only avoid iron therapy.

Q. What are the **complications** of repeated blood transfusion?

A. As follows:

- Repeated transfusion may cause hemosiderosis (usually when more than 30 to 50 L of blood is transfused).
- Infections such as hepatitis B, C, D and HIV.

Q. How hemosiderosis can be **prevented**?

A. Hemosiderosis can be prevented by using chelating agent desferrioxamine (1.5 to 2 g with each unit of blood). It is usually given subcutaneously in the anterior abdominal wall with infusion pump for 12 hours. It may also be given with infusion drip (normal saline or aqua). Oral chelating agent

such as deferiprone, 75 mg/kg in 2 to 4 divided doses, is also available. Other oral chelating agent include deferasirox. Vitamin C 200 mg daily orally also helps in iron excretion.

Q. If the patient develops severe **abdominal pain**, what is the likely cause?

A. Cholelithiasis (usually pigment stone, due to hemolysis). There may also be splenic infarction. Acute pancreatitis may also occur.

Q. When **anemia** develops in a patient with thalassemia major?

A. Anemia develops at the age of 4 to 6 months. In a normal person, HbF disappears 4 to 6 months after birth. In adults, HbF is < 1%. But in thalassemia major, HbF is increased.

Q. How can it be **diagnosed before birth**?

A. Prenatal diagnosis is possible by obtaining chorionic villus material for DNA. It should be done if both parents suffer from β-thalassemia minor. If β-thalassemia is found in the fetus, then termination of pregnancy is indicated.

Q. What are the presentations of **thalassemia minor**? What is the **differential diagnosis**?

A. As follows:

- May be asymptomatic.
- There may be features of anemia (microcytic hypochromic).
- Incidentally during blood count (microcytic hypochromic blood picture).
- Hemoglobin electrophoresis shows high A_2.

Thalassemia minor confuses with iron deficiency anemia. However, anemia is more marked in iron deficiency and relatively less in thalassemia minor. Also, in iron deficiency, there is low iron, low ferritin and high total iron-binding capacity.

Brief discussion on α-thalassemia

This is characterized by reduced or absent α-globin chain synthesis. It is common in southeast Asia and China. Normally, adults have 4 α-globin chain genes.

- When one α-gene is absent the patient is hematologically normal (silent carrier).
- When two α-genes are absent it is said to have α-thalassemia trait. The patient is clinically normal, life expectancy is normal but there is mild microcytic hypochromic anemia.
- When three alpha genes are absent the patient has hemoglobin H (β-chain tetramer) disease. There is chronic hemolytic anemia with variable severity. Physical examination shows severe anemia with splenomegaly.
- If all four α-globin chains are absent affected fetus is stillborn due to hydrops fetalis.

IDIOPATHIC THROMBOCYTOPENIC PURPURA

CHIEF COMPLAINTS

- Multiple spots on the skin all over the body for … days
- Anorexia, malaise and weakness for … days.

HISTORY

History present illness: The patient states that she was alright … days back. Since then, she noticed multiple red spots which first appeared in the arms and legs, subsequently involving the other parts of the body. These were initially red, which became bluish and black after few days. There are also some larger bleeding areas in different parts of the body. She also complains of loss of appetite, malaise and weakness for the same duration. There is no history of fever, sore throat, polyarthritis, skin rash, abdominal pain or mouth ulcer. She did not take any drug prior to the illness. Her bowel and bladder habits are normal.

History of past illness: There is no history of bleeding disorder.

Family history: There is no history of any bleeding disorder in the family.

Personal history: Mention as per statement of the patient.

Socioeconomic history: Mention as per statement of the patient.

Drug and Treatment history: There is no history of intake of any drug related to his symptoms.

GENERAL EXAMINATION

- The patient is mildly anemic
- There are multiple purpuric spots on different parts of the body of varying sizes, which are painless, do not blanch on pressure
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- No sternal tenderness
- Pulse: 120/min
- BP: 100/55 mm Hg.

SYSTEMIC EXAMINATION

Gastrointestinal System

- Lips and oral cavity—There are some bleeding spots over the palate
- Tongue—Normal.

Abdomen

Inspection:

- No abnormality.

Palpation:

- Liver—not palpable
- Spleen—not enlarged
- Kidneys—not ballotable.

Percussion:

- No evidence of ascites (no fluid thrill, no shifting dullness).

Auscultation:

- No abnormality detected.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Ms …, 19 years old, student, normotensive, nondiabetic, nonsmoker, hailing from …, presented with multiple red spots for … days. These first appeared in the arms and legs, subsequently involving the other parts of the body. These were initially red, which became bluish and black after few days. There are also some larger bleeding areas in different parts of the body. She also complains of loss of appetite, malaise and weakness for the same duration. There is no history of fever, sore throat, polyarthritis, skin rash, abdominal pain or mouth ulcer. She did not take any drug prior to the illness. Her bowel and bladder habits are normal. There is no history of bleeding disorder. There is no history of any bleeding disorder in the family.

On general examination (mention as above).

On systemic examination (mention as above).

With this history and physical findings, I have some differential diagnoses:

- Idiopathic thrombocytopenic purpura
- Acute leukemia
- Aplastic anemia.

Q. What is the more likely diagnosis? Why?

A. Idiopathic thrombocytopenic purpura. Because, there are multiple purpuric spots, no history of taking any drugs or secondary causes.

Q. Why not acute leukemia?

A. It may be acute leukemia, but less likely because there is no fever, lymphadenopathy, hepatosplenomegaly and bony tenderness.

Q. Why not aplastic anemia?

A. There is no history of any secondary cause like drugs, radiation, etc. Usually there is severe anemia, bleeding is usually in the form of ecchymoses or bruises. But it should be excluded.

Q. What investigations do you suggest in ITP?

A. As follows:

- Full blood count—there is thrombocytopenia
- Bone marrow—increased immature megakaryocytes (may be normal sometimes)
- Bleeding time is prolonged, but clotting time is normal
- Antiplatelet antibody is present in 60 to 70% cases
- Anticardiolipin antibody is positive in 30% cases.

Q. What are the causes of thrombocytopenia?

A. As follows:

1. Less production:
   - Aplastic anemia (primary or idiopathic)

- Bone marrow infiltration—secondary deposit, multiple myeloma, leukemia, lymphoma
- Marrow suppression by radiotherapy or cytotoxic drugs
- Megaloblastic anemia
- Myelofibrosis
- HIV infection.

2. Excessive destruction or consumption:
   - Immune—ITP, drug induced (heparin, thiazide, penicillin, quinine), SLE, CLL, virus, post-transfusional.
   - Nonimmune—DIC, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, hypersplenism, massive blood transfusion (dilutional).

RELATED QUESTIONS AND ANSWERS

Q. What is **idiopathic thrombocytopenic purpura?**

A. It is a type of thrombocytopenic purpura due to auto-antibody against platelet (IgG type). The auto-antibody forms against platelet membrane glycoprotein IIb and IIIa, which causes premature removal of platelet by monocytemacrophage system.

Q. What are the **presentations** of ITP?

A. As follows:

- In child—Usually acute presentation, previous history of viral infection followed by bleeding or purpura, easy bruising, etc. Chronic ITP is rare in children.
- In adult—common in female, usually insidious onset without preceding viral infection. Presents with purpura, easy bruising, epistaxis or menorrhagia. Features of SLE may be present at presentation or may develop after long time. It may be associated with other autoimmune diseases like thyroid disorder and autoimmune hemolytic anemia, chronic lymphocytic leukemia, solid tumor, HIV infection.

On physical examination—apart from bleeding points, no other physical findings. Splenomegaly is very rare (in 10%).

Note Remember the following points:

- Spontaneous bleeding occurs when the platelet is < 20,000/cmm
- At higher count, there may be bruising, epistaxis and menorrhagia
- If platelet count is > 50,000/cmm, there may not be any features, diagnosed on routine test.

Q. What are the **diseases to be excluded**, if ITP is suspected?

A. As follows:

1. Commonly SLE is to be excluded. In 10% cases, thrombocytopenia may be the initial manifestation of SLE for many years.
2. Primary antiphospholipid syndrome may present with thrombocytopenia.
3. Other primary hemorrhagic disorders should be excluded.
4. For this purpose, following investigations should be done—
   - ANA, anti ds-DNA, antiphospholipid antibody and anticardiolipin antibody
   - Bone marrow

Note Remember these points:

- In 10% case, ITP may be associated with autoimmune hemolytic anemia called **Evan's syndrome**.
- Patient > 65 years old should have bone marrow examination to look for accompanying B-cell malignancy.
- HIV testing should be considered, if there is strong suspicion.

Q. How to **treat** ITP?

A. Treatment is as follows:

i. In child: Usually self limiting, does not require treatment in most cases. If there is no improvement—

- Prednisolone (2mg/kg) should be given if moderate to severe thrombocytopenia (<10,000) and bruising, epistaxis or other bleeding.
- If still persistent bleeding, IV immunoglobulin (IgG) should be given.
- In some case, platelet transfusion may be required, when there is persistent bleeding (epistaxis, GIT bleeding, retinal hemorrhage, intracranial bleeding).

ii. In adult: Persistent thrombocytopenia is common. Most patients with platelet count > 30×10^9/L are stable and do not require treatment unless they are about to undergo a surgery.

1. First line therapy:
   - If spontaneous bleeding, prednisolone 1mg/kg, to be given for 4 to 6 weeks, then tapered. 66% will respond, but relapse is common when the steroid dose is reduced or stopped. 10 to 20% usually have long term remission. If relapse, steroid should be started again.
   - IV immunoglobulin may be given, mainly if there is severe hemostatic failure or slow response to steroid alone or surgery is required. Dose of immunoglobulin is 1gm/kg for 3 to 5 days. Its effect is temporary, persists for 3 to 4 weeks and it is quite expensive. Steroid may be added with immunoglobulin.
2. Second line therapy:
   - If there is frequent relapse (usually 2 relapses), in primary refractory disease or require high dose of steroid to maintain safe platelet level, splenectomy should be done. There is complete remission in 70% cases and improvement in 20 to 25% cases. 5 to 10% require further medical therapy.
3. Third line therapy:
   - If there is failure after splenectomy, other therapy should be considered—corticosteroid, IV immunoglobulin, anti-D infusion, danazol, immunosuppressive therapy (azathioprine, cyclophosphamide, dapsone, vincristine, vinblastine, ciclosporin), mycophenolate mofetil. Also monoclonal antibody like rituximab as well as recombinant thrombopoietin may be given.
4. Platelet transfusion is not usually used. However, it is used only if persistent or potentially life threatening bleeding or where emergency splenectomy is done.

Note Remember the following points

- In nonresponder after splenectomy, think of presence of accessory spleen (confirm by radionuclide scan).
- After splenectomy, there is more chance of infection by *Pneumococcus*, *Meningococcus* and *H. influnzae* (vaccination against these is essential).

Q. What are the **differences** between ITP in children and adults (or acute and chronic ITP)?

A. As follows:

Features	Child (acute)	Adult (chronic)
1. Age	Usually 2 to 6 years	20 to 30 years
2. Sex	Any	Common in female
3. Onset	Acute	Chronic
4. Previous infection	Common	Unusual
5. Platelet count	<20,000/cmm	>20,000/cmm
6. Spontaneous remission	Common	Less <20%
7. Duration	2 to 4 weeks	Chronic, months to years

BRIEF DISCUSSION ON PURPURA

Q. What is **purpura**? What are the **types**?

A. It is the spontaneous bleeding or extravasation of blood from the capillary in the skin and mucous membrane that does not blanch on pressure, and there is progressive color change.

There are **two types** of purpura:

- Small and discrete of pin head size, called petechiae.
- Large and ill defined, called ecchymosis.

Q. What are the **causes of purpura?**

A. As follows:

- Thrombocytopenic
- Vascular
- Coagulation defect.

Thrombocytopenic purpura:

1. Primary or ITP.
2. Secondary:
   - Aplastic anemia (due to any cause)
   - Leukemia
   - Secondary deposit in bone marrow
   - SLE
   - Others—DIC, CLD and TTP (thrombotic thrombocytopenic purpura), massive blood transfusion.

Vascular purpura:

1. Congenital (hereditary hemorrhagic telangiectasia, Ehlers–Danlos syndrome).
2. Acquired:
   - Senility (in elderly)
   - Henoch-Schönlein purpura (in children, and rarely in elderly)
   - Drug-induced (NSAIDs, thiazide, steroid, sulfonamide, penicillin and thiouracil)
   - Infections—SBE, typhoid, meningococcal infection, septicemia and viral infections (infectious mononucleosis, measles, chicken pox, dengue hemorrhagic fever)

- Scurvy
- Metabolic disorder (CRF and Cushing's syndrome)
- Collagen disease (RA and SLE)
- Paraproteinemia (purpura is due to vasculitis or thrombocytopenia or platelet functional abnormality)
- Amyloidosis (periorbital).

Coagulation abnormality:

1. Hemophilia.
2. Christmas disease.
3. Anticoagulant therapy.

Q. What are the common **causes of** purpura according to the age?

A. As follows:

1. In the **elderly**, the causes are:
   - Senile purpura (usually on extensor surface of forearm and leg).
   - Drug induced purpura (distribution is like senile purpura), and the usual drugs are steroids, NSAIDs and anticoagulant.
   - Leukemia.
   - Aplastic anemia.
   - Scurvy.
   - Paraproteinemia.
2. In **young** or **child**, the causes are:
   - ITP
   - Henoch-Schönlein purpura (involving buttock and legs)
   - Drug induced
   - Acute leukemia
   - Infections—viral (dengue) or meningococcal septicemia.

Note In any age, mention the causes as follows (if present):

- If Cushingoid facies, due to steroid
- If patient looks toxic, due to septicemia
- If evidence of RA, SLE, due to disease itself or due to NSAIDs or steroids.

Q. In a child, there is purpura in the leg. What **else** do you want to see?

A. Purpura in buttock, history of arthritis, abdominal pain, bloody diarrhea, hematuria (all features are suggestive of Henoch-Schönlein purpura).

Q. What should you **examine** in a patient with purpura?

A. As follows:

1. Whether they blanch on pressure or not (purpura does not blanch).
2. Whether they are palpable and painful or not (palpable painful purpura is of vascular origin and nonpalpable purpura indicates thrombocytopenia).
3. Color change (progressive color change in purpura from red to dark pigmented).
4. Distribution of purpura:
   - Buttock, ankle (Henoch-Schönlein purpura).
   - Extensor surface of fore arm, dorsum of hand, leg (senile purpura and drugs).
   - Generalized purpura.

Q. What are the **differential diagnoses** of purpura?

A. As follows:

- Drug rash
- Spider angioma or telangiectasia (blanch on pressure, but purpura does not)
- Erythema nodosum (painful and nodular)
- Mosquito bite (usually blanch on pressure, but sometimes may not blanch, if there is extravasation of blood)
- Campbell de Morgan spots (common in elderly)—these are small, nodular, reddish lesions that do not blanch on pressure, occur on trunk and upper abdomen and resolve spontaneously. These are benign angioma, common in middle aged and elderly. Malignant change occurs rarely (suggested by itching, rapid increase in size and increased pigmentation).

Q. What **investigations** should be done in purpura?

A. As follows:

1. Hb%, TC, DC, ESR, platelet and PBF.
2. If pancytopenia or thrombocytopenia, perform bone marrow study (dry tap in aplastic anemia, increased megakaryocyte in ITP).
3. Other investigations (according to suspicion of causes):
   - Coagulation screen (BT, CT, PT, APTT and FDP) for hemophilia and Christmas disease and other coagulation factors, screening for DIC.
   - Blood culture (if septicemia).
   - ANA, anti-double-strand DNA (for SLE).
   - Anti-phospholipid antibody.
   - Liver function tests (in CLD).
   - Renal function tests (in CRF).

Q. What is **Hess's test**?

A. It is a bedside test, also called tourniquet test. In this test, a sphygmomanometer cuff over the upper arm is inflated in between systolic and diastolic pressure, wait for 5 minutes. Then deflate the cuff, wait for another 5 minutes. Look for petechiae in cubital fossa and near the wrist. Normally, there may be <5. If >10, it is an indication of thrombocytopenia. If >20, then abnormal. If platelet is <60,000, it is usually positive.

Causes: Thrombocytopenia or platelet functional abnormality or increase in capillary fragility (This test is frequently done to diagnose dengue hemorrhagic fever).

Q. What are the **causes** of platelet functional abnormality?

A. Platelet functional abnormality (thrombasthenia) occur in:

- Chronic renal failure
- Chronic liver disease
- Paraproteinemia
- Myeloproliferative diseases
- Drugs—NSAIDs (aspirin, indomethacin and ibuprofen).

Q. How to **differentiate** in bleeding or purpura whether due to bleeding abnormality or coagulation abnormality?

A. As follows:

Coagulation abnormality	Bleeding abnormality
1. Family history usually present	Family history may or may not be present
2. There is history of prolonged bleeding	No history of prolonged bleeding
3. Usually there is bleeding into the joint or muscle, purpura is less common or rare	Bleeding into the skin and mucous membrane, purpura is more common
4. Clotting time is prolonged, but bleeding time and platelet count are normal	Clotting time is normal, but bleeding time is prolonged and platelet count is low
5. Particular coagulation factor is low or absent, e.g. in hemophilia, factor VIII is absent or low	Coagulation factor is normal, and it is due to either low or defect in platelet function or vascular defect

HENOCH-SCHONLEIN PURPURA

CHIEF COMPLAINTS

- Multiple skin rashes over lower limbs for … days
- Pain in abdomen for … days
- Joint pain for … days
- Low grade fever, anorexia, weakness for … days.

HISTORY

History present illness: The patient states that he was alright … days back. Since then, he noticed multiple red spots involving both lower limbs. These were initially red, which became bluish and black after few days. The lesions are painful but not itching. He also complains of occasional colicky abdominal pain for … days, which is not related to any food and there is no radiation. It is associated with loose motion, mixed with fresh blood. For the last … days, he has been suffering from pain and swelling of both knee joints, which is very severe and aggravates on movement. The patient also complains of low grade continued fever, lost his appetite and become very weak for the same duration. There is no history of mouth ulcer, sore throat, photosensitivity, etc. His bladder habit is normal.

History of past illness

Family history

Personal history

Socioeconomic history

Drug and treatment history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient looks ill, mildly anemic.
- There are multiple purpuric spots on both lower limbs, including buttocks. These are of variable size and shape, palpable, painful and don't blanch on pressure.
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema.
- No lymphadenopathy or thyromegaly.
- No sternal tenderness.
- Pulse: 120/min.
- BP: 100/55 mm Hg.

SYSTEMIC EXAMINATION

Gastrointestinal System

- Lips and oral cavity—There are some bleeding spots in palate
- Tongue—Normal.

Abdomen

Inspection:

- No abnormality.

Palpation:

- Diffusely tender.
- Liver—not palpable.
- Spleen—not enlarged.
- Kidneys—not ballotable.

Percussion:

- No evidence of ascites (no fluid thrill, no shifting dullness).

Auscultation:

- No abnormality detected.

Locomotor System

- Both knees and ankle joints are swollen and painful
- Movement is restricted.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 14 years old, student, normotensive, nondiabetic, hailing from …, presented with multiple red spots involving both lower limbs for … days. These were initially red, which became bluish and black after few days. The lesions are painful but not itching. He also complains of occasional colicky abdominal pain for … days, which is not related to any food and there is no radiation. It is associated with loose motion, mixed with fresh blood. For the last … days, he has been suffering from pain and swelling of both knee joints, which is very severe and aggravates on movement. The patient also complains of low grade continued fever, lost his appetite and become very weak for the same duration. There is no history of mouth ulcer, sore throat, photosensitivity, etc. His bladder habit is normal. There is no family history of similar illness. He was treated with ranitidin, antispasmodics and vitamins.

On general examination (mention as above).

On systemic examination (mention as above).

My diagnosis is Henoch-Schonlein purpura.

Q. Why this is Henoch-Schönlein purpura?

A. There is history of arthritis, abdominal pain and bloody diarrhea. On examination, there are multiple purpuric skin rash involving lower limbs and buttocks. All are suggestive of Henoch-Schonlein purpura.

Q. What are your differential diagnoses?

A. As follows:

- Drug rash
- ITP
- SLE
- Septicemia
- Thrombotic thrombocytopenic purpura (TTP).

Q. Why not this is a case of ITP?

A. In ITP, there may be previous history of viral infection followed by purpura only. There is no arthritis or abdominal pain in ITP.

Q. What **investigations** should be done in HSP?

A. As follows:

- Full blood count and platelet (nonthrombocytopenic purpura).
- Urine (proteinuria and hematuria).
- Serum IgA is high in 50% cases (IgA-containing immune complex is also high).
- Skin biopsy from normal and involved skin (it will show leukocytoclastic vasculitis with deposition of IgA and complement C_3 in blood vessels).
- Kidney biopsy.

Q. Suggest one **investigation** that is helpful for prognosis.

A. Renal biopsy—it shows focal and segmental proliferative glomerulonephritis, sometimes with mesangial hypercellularity. In more severe cases, epithelial crescents may be present, developing rapidly progressing glomerulonephritis and renal failure. This is less in children. There is IgA deposition within and around blood vessels, glomerular mesangium (it may be confused with IgA nephropathy).

Prognosis of HSP: It is related to the severity of renal involvement.

RELATED QUESTIONS AND ANSWERS

Q. What is **Henoch–Schönlein purpura** (anaphylactoid purpura)?

A. It is a small vessel vasculitis characterized by purpura or skin rash, joint pain (in big joints), abdominal pain and glomerulonephritis. It is a type III reaction precipitated by an upper respiratory tract infection (usually viral) that occurrs 1 to 3 weeks ago.

It is due to circulating IgA - containing immune complex. Occurs 1 to 3 weeks after upper respiratory infection (usually viral). Other factors responsible include food, drugs or vaccination.

Q. What are the **clinical features** of HSP?

A. HSP is more common in boy, 5 to 15 years of age, but may occur in any age. The common features are:

- Skin lesion—Purpura is common in legs and buttock, face and trunk are spared. May resolves in 2 to 4 weeks and fresh crops may appear. Angioedema occurs in 50% cases.
- Polyarthritis occurs in 70%, commonly involves knee and ankle, may be fleeting type.
- Abdominal pain, colicky in nature, associated with nausea, vomiting, bloody diarrhea, intussusception and perforation. There is vasculitis, bowel is edematous and inflamed, causing bleeding and obstruction. This may be confused with acute surgical condition.
- Renal disease occurs in 30 to 70% cases, present with hematuria and proteinuria. It is usually mild. There may be nephrotic syndrome and rarely renal failure.

Q. How will you **treat** a patient with HSP?

A. As follows:

- It is usually self-limiting, spontaneous cure in majority of cases.
- Steroid is indicated, if there is GIT and joint symptoms. However, steroid does not affect the course and progression of disease. Abdominal pain may be improved in 24 hours following the use of steroid.
- In renal involvement, pulse IV steroid and cytotoxic drugs should be given.
- Recurrence may occur. If so, dapsone may help, specially in cutaneous recurrence.

Q. What is the **prognosis**?

A. Good in children, relatively bad in adults. Adverse factors in adults include hypertension, abnormal renal function and proteinuria > 1.5 g/day. But only 1% of patients develop end stage renal failure.

Features of Henoch-Schönlein purpura in adults:

- Skin involvement is common (70%), more than children
- Renal involvement is more common than children
- Gut and joint involvement occur in 20% cases, less than children
- Myocardial involvement may occur rarely
- Prognosis is worse in adults than children.

Note Remember the following:

In children, gastrointestinal vasculitis is more common, renal and skin involvement are less common. Prognosis is better.

HEMOPHILIA

CHIEF COMPLAINTS

- Persistent bleeding after injury since childhood
- Occasional swelling of right knee since childhood.

HISTORY

History present illness: According to the mother of the patient, she noticed that her son has been suffering from persistent and prolong bleeding from any injury since his childhood. There is also history of prolonged and profuse bleeding after circumcision and one tooth extraction. The patient's mother also states that following trauma or fall, there are multiple bruises in different parts of the body. Occasionally, his right knee is swollen after trauma or physical exertion and become painful. There is no history of bleeding from nose, gum or passage of black stool.

History of past illness: Mention according to the statement of the patient.

Family history: One of his maternal uncle also has similar history of prolong bleeding after any injury.

Personal history: Mention according to the statement of the patient.

Socioeconomic history: Mention according to the statement of the patient.

Drug and treatment history: For this illness, the patient received multiple blood transfusions over last few years.

GENERAL EXAMINATION

- The patient is mildly anemic
- There are multiple bruises over the trunk and legs
- The right knee is swollen and tender
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- No sternal tenderness
- Pulse: 100/min.
- BP: 100/60 mm Hg.

SYSTEMIC EXAMINATION

Gastrointestinal System

- Lips, tongue and oral cavity—normal.

Abdomen

Inspection:

- No abnormality.

Palpation:

- Liver—not palpable
- Spleen—not enlarged
- Kidneys—not ballotable.

Percussion:

- No evidence of ascites (no fluid thrill, no shifting dullness).

Auscultation:

- No abnormality detected.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr. …, 14 years old boy, student, hailing from …, presented with persistent and prolong bleeding from any injury since his childhood. There is also history of prolonged and profuse bleeding after circumcision and one tooth extraction. The patient's mother also states that following trauma or fall, there are multiple bruises in different parts of the body. Occasionally, his right knee is swollen after trauma or physical exertion and become painful. There is no history of bleeding from nose, gum or passage of black stool. One of his maternal uncles also has similar history of prolong bleeding after any injury. For this illness, the patient received multiple blood transfusions over last few years.

On examination, general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is hemophilia.

Q. What are your **differential diagnoses?**

A. As follows:

- Christmas disease
- ITP.

Q. **Why not** this is ITP?

A. In ITP, there should be no persistent bleeding, only purpura. No joint pain also.

Q. What **investigations** are done in hemophilia?

A. As follows:

- FBC—usually normal
- Bleeding time, prothrombin time, platelet count, von Willebrand factor (vWF) and fibrinogen level—all normal
- Clotting time and activated partial thromboplastin time (APTT) are prolonged
- Factor VIII: C assay—deficient or absent
- X-ray of the involved joints, if needed.

Note Remember the following:

APTT is prolonged, which is corrected by addition of normal plasma. If not corrected after the addition of normal plasma, more likely there is antibody formation or the presence of antiphospholipid antibody.

Q. Is **antenatal** diagnosis possible?

A. Yes. Antenatal diagnosis may be done by molecular analysis of fetal tissue obtained by chorionic villous biopsy at 11 to 12 weeks of pregnancy.

RELATED QUESTIONS AND ANSWERS

Q. What is **hemophilia**?

A. It is an X-linked inherited disorder due to deficiency of factor VIII or antihemophilic factor, characterized by prolonged bleeding. Male is the sufferer, female is the carrier.

Q. What are the **types** of hemophilia?

A. Normal factor VIII level is 50 to 150 IU/dL. According to severity, it is of 3 types—

1. Mild—factor VIII is 10 to 50% (> 5 but < 40 IU/dL). Bleeding occurs following injury or surgery.
2. Moderate—factor VIII is 2 to 10% (1 to 5 IU/dL). There is severe bleeding following injury or surgery, also spontaneous bleeding sometimes.
3. Severe—factor VIII is <2% (<1 IU/dL). There is frequent spontaneous bleeding, also bleeding into the joints and muscles.

Q. What is the **pedigree** of hemophilia?

A. As follows:

1. If father is affected:
- All daughters are carriers
- All sons are normal.

2. If mother is carrier:
- 50% daughters are carriers
- 50% sons are sufferers.

Note Remember the following points:

- In a female carrier, factor VIII is < 50% of normal, because of randomised inactivation of one X chromosome.
- Usually female is the carrier and male is the sufferer.

Q. Can a **female be** the **sufferer** in hemophilia?

A. Yes, rarely a female can be a sufferer, because of the following reasons:

- If a carrier female is married to an affected male, the female baby may be a sufferer.
- According to lyonisation theory, there is randomized inactivation of one X chromosome in the developing fetus. Then the number of affected X chromosome may be predominant. Female may be affected, if normal X chromosome is disproportionately inactivated.
- Turner's syndrome (because there is XO, if the only X is affected).

Q. How the patient usually **presents**?

A. Depends on whether factor VIII deficiency is mild, moderate or severe

- Prolonged and persistent bleeding after trauma or injury, tooth extraction
- Sometimes, spontaneous bleeding may occur in severe cases
- Bleeding into the large joints and muscles (psoas and calf muscle) is also common.

Q. What happens if the patient has **bleeding into the psoas muscle**?

A. As follows:

- Severe pain in lower abdomen
- Paresthesia in thigh and weakness of quadriceps due to compression of femoral nerve.

Q. What are the **complications** of hemophilia?

A. As follows:

1. Due to repeated hemorrhage:
   - Arthropathy due to repeated bleeding in joint (e.g. knee, elbow)
   - Atrophy or wasting of muscles secondary to hematoma in muscle
   - Mononeuropathy due to pressure by hematoma
   - Death may occur due to intracerebral hemorrhage.
2. Due to therapy:
   - Infections—hepatitis A, B, C, D. Also, HIV
   - Factor VIII antibody (20 to 30%).

Q. How will you **manage** hemophilia?

A. As follows:

1. Bleeding episodes are treated with intravenous infusion of factor VIII concentrate, usually two to three times daily (its half life is 12 hours).
   - For minor bleeding—factor VIII level should be raised to 20 to 30 IU/dL.
   - Severe bleeding—factor VIII should be raised to at least 50 IU/dL.
   - Major surgery—factor VIII should be raised to 100 IU/dL preoperatively and maintained above 50 IU/dL until healing has occurred.
2. If factor VIII is not available, cryoprecipitate, fresh frozen plasma or fresh blood can be given.
3. Synthetic vasopressin (desmopressin—an analog of vasopressin)—intravenous, subcutaneous or intranasal, produces a rise in factor VIII:C. It avoids the complications associated with blood products and is useful for treating bleeding episodes in mild hemophilia and as prophylaxis before minor surgery. It is ineffective in severe hemophilia. Repeated use of desmopressin may cause water retention leading to hyponatremia.
4. Genetic counceling.

Note Remember the following points:

- Factor VIII was initially prepared from plasma. It is now prepared from recombinant DNA technology (there is less risk of transfusion transmitted infection but more expensive).
- Advice to the patient—avoid trauma, NSAIDs and IM injection. Precaution should be taken before tooth extraction and surgery.

Q. If factor VIII **antibody** develops, how can it be suspected and treated?

A. Upto 30% cases with severe hemophilia may develop antibodies to factor VIII that inhibits its action. It is suspected if there is no response to factor VIII therapy. This antibody rarely develops in mild and moderate hemophilia, often disappears spontaneously or with continued treatment.

It is very difficult to treat when antibody develops. Following options are available:

- Increasing the dose and frequency of factor VIII therapy. It may or may not be helpful.
- Factor IX may be used. It helps bypassing the inhibitors.
- Recombinant factor VIIa—helps bypassing the inhibitors.
- Factor VIII inhibitor bypassing activity (FEIBA—an activated concentrate of factors II, IX and X).
- Sometimes, immunosuppressive therapy such as steroid, azathioprine or cytotoxic drugs may be given.

Brief notes on Hemophilic Arthritis

Q. What are the **presentations** of hemophilic arthritis?

A. Hemarthrosis occurs when plasma level of factor VIII: C is < 1%. Arthritis may be spontaneous without trauma or may follow even minor trauma.

- Initially, tingling, abnormal sensation, stiffness and instability of the joint.
- Later on, the joint is red, hot, swollen and painful.

Progression of arthritis depends on repeated hemarthrosis which leads to:

- Synovium hypertrophy
- Fibrotic change in synovium
- Destruction of cartilage
- Reduction of joint space
- Subchondral cyst formation
- Bone shows erosion, marginal sclerosis, osteophyte formation and ankylosis of joint.

Q. Which **joints are commonly involved** in hemophilic arthritis?

A. Commonly knee, elbow, ankle and hip joints are involved.

- In infants—hip joint is commonly involved.
- In older children—knee joint is commonly involved.

Q. What are the **radiological signs** in hemophilic arthritis?

A. As follows:

- Initially, joint space is increased and widening of intercondylar notch occurs (in knee joint, indicates long-standing hemorrhage).
- Later on—there is reduction of joint space, periarticular osteopenia, marginal sclerosis, subchondral cyst formation, secondary osteoarthrosis (with osteophyte) and ankylosis of joint.

Q. What are the causes of **widening** of intercondylar notch?

A. As follows:

- Hemophilia
- Christmas disease
- Long-standing effusion in knee joint.

Q. What are the causes of **hemarthrosis**?

A. As follows:

- Trauma
- Hemophilia
- Christmas disease
- Von Willebrand's disease
- Others—sickle cell disease, excess anticoagulant, rarely malignancy.

Q. How to **treat** hemophilic arthritis?

A. As follows:

- Complete rest, if needed splinting of joint.
- Factor VIII transfusion—20 to 30 IU/kg. It is repeated after 12 hours, also after 24 and 36 hours (higher dose is required, if treatment is delayed).
- For pain—COX 2 inhibitors like celecoxib may be used. Orally opioid may be given.
- Physiotherapy—once bleeding is settled, mobilization and physiotherapy should be started. Usually, after 48 hours (isometric exercise, followed by active movement, and hydrotherapy or short wave diathermy).
- Arthrocentesis is rarely necessary, but in some cases with massive bleeding, aspiration of blood from joint followed by factor VIII therapy may be needed.
- To prevent recurrent bleeding into the joint—the patient with severe hemophilia are given factor VIII infusions regularly 3 times per week.

ANEMIA

CHIEF COMPLAINTS

- Weakness for … months
- Occasional dizziness for … months
- Tingling and numbness in lower limbs for … months
- Anorexia, weight loss and palpitation for … months.

HISTORY

History present illness: The patient states that she was alright … months back. Since then, she has been suffering from severe weakness which is gradually worsening and now she finds it difficult to perform regular daily activities. For the last … months, she also experiences occasional dizziness, light-headedness, tingling and numbness in both feet and occasional cramps in calf muscles. The patient also complains of palpitation, loss of appetite and weight loss for … months. There is no history of fever, difficulty in swallowing, bleeding from any sites or menorrhagia and bowel or bladder abnormality.

History of past illness

Family history

Personal history

Menstrual history

Socioeconomic history

Drug history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient looks pale
- Moderately anemic
- No jaundice, clubbing, cyanosis, koilonychia, leukonychia or edema
- No lymphadenopathy or thyromegaly
- Sternal tenderness: Absent
- Pulse: 120/min.
- BP: 95/65 mm Hg.

SYSTEMIC EXAMINATION

Gastrointestinal System

- Tongue is smooth, shiny with atrophy of papillae
- Lips, gums, teeth, oral cavity and tonsils—normal.

Abdomen

Inspection:

- No abnormality.

Palpation:

- Diffusely tender
- Liver—not palpable
- Spleen—not enlarged
- Kidneys—not ballotable.

Percussion:

- No evidence of ascites (no fluid thrill, no shifting dullness).

Auscultation:

- No abnormality detected.

Cardiovascular System

- There is a systolic murmur in the apical area (likely to be flow murmur).

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mrs. …, 40 years old, housewife, normotensive, nondiabetic, nonsmoker, hailing from …, presented with severe weakness for … months, which is gradually worsening and now she finds it difficult to perform regular daily activities. For the last … months, she also experiences occasional dizziness, light-headedness, tingling and numbness in both feet and occasional cramps in calf muscles. The patient also complains of palpitation, loss of appetite and weight loss for … months. There is no history of fever, difficulty in swallowing, bleeding from any sites or menorrhagia and bowel or bladder abnormality. The patient was treated by local physicians with iron tablets, multivitamin and ranitidin. There is no family history of similar illness.

On examination—general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is moderate anemia for which I have some differential diagnoses:

- Iron deficiency anemia
- Megaloblastic anemia
- Acute leukemia.

Q. What is **anemia**?

A. Anemia is a clinical condition characterized by reduced hemoglobin concentration, which is usually but not invariably associated with reduced RBC.

RELATED QUESTIONS AND ANSWERS

Q. **Classify** anemia.

A. Anemia may be classified in two ways—etiological (based on cause) and morphological (based on morphology of RBC).

Etiological:

1. Hemorrhagic anemia (due to blood loss):

- Acute—Trauma, postpartum bleeding, hematemesis, melena, epistaxis.
- Chronic—Hook worms, hemorrhoids, excessive menstrual loss, bleeding peptic ulcer, etc.

2. Dyshemopoietic anemia (due to inadequate production of RBC):
   - Deficiency anemia—Iron, vitamin B_{12}, folate deficiency.
   - Aplastic anemia (bone marrow failure which may be primary or secondary to some other diseases or drugs).
   - Anemia of chronic disorder (ACD)—SLE, rheumatoid arthritis, CRF.
   - Others—Hypothyroidism, sideroblastic anemia, malignancy.
3. Hemolytic anemia:
   - Genetic—Red cell membrane defect (e.g. hereditary spherocytosis, eliptocytosis, stomatocytosis), hemoglobin abnormality (thalassemia, sickle cell anemia) or enzyme defects (glucose-6-phosphate dehydrogenase deficiency, pyruvate-kinase deficiency).
   - Acquired—Autoimmune, toxic, mechanical and infectious causes.

Morphological (depending on MCV and MCHC):
1. Normocytic normochromic anemia (normal MCV and MCHC).
2. Microcytic hypochromic anemia (low MCV < 76 fl, low MCHC < 30 g/dL).
3. Macrocytic anemia (high MCV > 96 fl).
4. Diamorphic anemia (two cell lines—macrocytes and microcytes).

Q. What are the causes of **normocytic normochromic anemia**?

A. As follows:
- Anemia of chronic disorder
- Chronic infection (e.g. tuberculosis)
- Collagen disease (e.g. SLE, rheumatoid arthritis)
- Malignancy
- Endocrine disease
- Sideroblasitic anemia.

Q. What are the causes of **microcytic hypochromic** anemia?

A. As follows:
- Iron deficiency anemia
- β-thalassemia major
- Sideroblastic anemia
- Anemia of chronic disorder (ACD).

Q. What are the causes of **macrocytic anemia**?

A. As follows:
1. Macrocytosis with megaloblastic marrow are found in:
   - Vitamin B_{12} deficiency
   - Folic acid deficiency.
2. Macrocytosis with normoblastic marrow are found in:
   - Chronic liver disease
   - Chronic alcoholism
   - Hypothyroidism
   - Hemorrhage
   - Hemolysis
   - Others—sideroblastic anemia, pure red cell aplasia, azathioprine therapy.

Q. What is **dimorphic anemia**? What are the **causes**?

A. When both microcytes and macocytes are found, this is called dimorphic anemia. Causes are:
- Combined iron, B_{12} and folate deficiency

- Sideroblastic anemia
- Treatment of anemia.

Q. What are the causes or mechanisms of **anemia of chronic disorder**?

A. Actual mechanism is unknown. It is due to abnormality of iron metabolism and erythropoiesis. There is less erythropoietin. Also red cell survival is short.

Q. What are the **signs** that may point to a specific cause of anemia?

A. As follows:

Sign	Cause of anemia
1. Triad of anemia, jaundice and splenomegaly	Hemolytic anemia
2. Angular cheilitis, glossitis, koilonychia	Iron deficiency anemia
3. Glossitis	Iron deficiency anemia, vitamin B_{12} deficiency, folate deficiency
4. Splenomegaly	Malaria, chronic hemolytic anemia, acute infection, leukemia, lymphoma, portal hypertension
5. Neurological changes (dementia, optic atrophy and features of subacute combined degeneration of spinal cord) and lemon yellow tint	Vitamin B_{12} deficiency (megaloblastic anemia)
6. Bony change (frontal and parietal bossing)	Hereditary hemolytic anemia
7. Leg ulcer	Sickle cell anemia, PNH
8. Bony tenderness	Acute leukemia, multiple myeloma, lymphoma, myelofibrosis

Q. What is **spurious anemia**?

A. When plasma volume is increased, hemoglobin is relatively low, it is called spurious anemia. It is found in pregnancy.

Q. What is **spurious polycythemia**?

A. Here hemoglobin is relatively increased due to low plasma volume. This is found in dehydration.

Q. How to **investigate** a patient with anemia?

A. Detailed history, physical examination and finally relevant laboratory investigations are done to investigate a patient with anemia.

History of the patient:

- Dietary history (to diagnose deficiency anemia like iron, vitamin B_{12} and folic acid deficiency).
- Malabsorption.
- Any history of bleeding (hemorrhoid, epistaxis, hematemesis, melena, menorrhagia in female, etc.).
- In female—multiple pregnancies, repeated abortion.
- Drug history—NSAIDs, steroid, drugs causing bone marrow suppression (e.g. cytotoxic drugs), drugs causing hemolysis (e.g. sulfasalazine, methyldopa, etc.).

- History of surgery—gastrectomy or partial gastrectomy, ileal surgery (responsible for vitamin B_{12} absorption).
- Family history (in case hereditary hemolytic anemia).
- History of any chronic disease (e.g. SLE, CRF, etc.).

Clinical examination—See the box above.

Laboratory investigations:

1. Full blood count (Hb%, TC, DC, ESR, platelet count):
   - Pancytopenia—which may be due to aplastic anemia, hypersplenism, megaloblastic anemia, aleukemic leukemia.
2. PBF examination: Following findings may be found which indicates particular causes of anemia (see below in the table).
3. Reticulocyte count: High in hemolytic anemia.
4. MCV and MCHC.
5. Bone marrow examination: Megaloblastic anemia, aplastic anemia, bone marrow infiltration (secondary deposit), ring sideroblasts (in sideroblastic anemia).
6. Other investigations in relation to suspicion and primary cause of diseases.

Further investigation of microcytic hypochromic anemia (low MCV and low MCHC):

- For iron deficiency anemia—Serum iron, TIBC, serum ferritin.
- For hereditary hemolytic anemia—Hemoglobin electrophoresis, skeletal survey.
- For sideroblastic anemia—According to history, bone marrow examination (ring sideroblasts)
- For anemia of chronic disease—Test should be done according to history of the patient.

Further investigations for macrocytic anemia (high MCV):

- Bone marrow is done. If megaloblast seen, serum B_{12} and folic acid assay should be done. If normoblast, further investigation should be according to history (see above).

Q. What diseases may be **diagnosed from PBF**?

A. As follows:

Finding	Description	Common diagnoses
1. Anisocytosis	Variation in size of RBC	Iron deficiency anemia, megaloblastic anemia, sideroblastic anemia
2. Poikilocytosis	Variation in shape of RBC	Iron deficiency anemia, thalassemia, sideroblastic anemia
3. Microcytosis	MCV < 76 fl	Iron deficiency anemia, thalassemia, sideroblastic anemia, anemia of chronic disorder
4. Macrocytosis	MCV > 100 fl	Vitamin B_{12} and folic acid deficiency, chronic liver disease, alcohol, hypothyroidism, zidovudine
5. Hypochromia	Central pallor of RBC is increased in size (lower hemoglobin content)	Iron deficiency anemia, thalassemia, sideroblastic anemia, anemia of chronic disorder

Contd...

Contd...

6. Basophilic stippling or punctate basophilia	Deep blue dots scattered in cytoplasm of RBC (seen with Romanowsky staining)	Chronic lead poisoning, dyshemopoiesis
7. Target cells	Flat red cells with a central mass of hemoglobin (dense area), surrounded by a ring of pallor (pale area) and an outer ring of hemoglobin (dense area)	Iron deficiency anemia, thalassemia, hemoglobic C disease, CLD, splenectomy
8. Howell-Jolly bodies	Small round remnants of nuclear material in RBC. These are normally removed by spleen	Hyposplenism, post splenectomy, dyshemopoiesis
9. Heinz's bodies (Ehrlich's bodies)	Formed from denatured aggregated hemoglobin in red cells (seen with supravital staining with brilliant cresyl blue)	Thalassemia, hemolysis in glucose 6 phosphate dehydrogenase deficiency, asplenia and CLD, drug like sulfasalazine, dapsone
10. Acanthocytes (spur cells)	RBC with irregular spicules	Abetalipoproteinemia
11. Burr cells	RBC with regularly placed spicules	CRF
12. Schistocytes	Fragmented RBC. These are found in microangiopathic hemolytic anemia	Causes—DIC, HUS, TTP, disseminated carcinomatosis, malignant or pregnancy induced hypertension (eclampsia)
13. Spherocytes	Small, densely packed RBC with loss of central pallor	Hereditary spherocytosis, autoimmune hemolytic anemia, post-splenectomy
14. Sickle cell	Sickle shaped	Sickle cell anemia
15. Blister cells		Glucose-6-phosphate dehydrogenase deficiency
16. Nucleated RBC	Normoblasts	Bone marrow infiltration, severe hemolysis, myelofibrosis, acute hemorrhage
17. Polychromatia	Young red cells, reticulocytes (bluish tinge)	Hemolysis, acute hemorrhage, increased red cell turnover

Q. What is **sideroblastic anemia**?

A. Sideroblastic anemias are inherited or acquired disorders characterized by refractory anemia, a variable number of hypochromic cells in the peripheral blood, and excess iron and ring siderblasts. Blood film usually shows microcytic anemia, may be dimorphic.

Classification:

1. Herediatry:
   a. X-linked disease, transmitted by females.

2. Acquried:
   a. Primary (one of the myelodysplastic syndromes).
   b. Secondary:
      - Inflammatory—rheumatoid arthritis
      - Neoplastic—lymphoma, leukemia, carcinoma, myeloproliferative disorders, multiple myeloma, carcinoma
      - Drugs—INH, pyrazinamide, cyclosporine
      - Alcohol abuse
      - Lead poisoning
      - Other disorders, e.g. megaloblastic and hemolytic anemias, malabsorption, severe malnutrition, erythroleukemia.

Treatment:

- Treatment of the primary cause, if present. For example, withdrawal of drug, stop alcohol intake, etc.
- Some case may respond to pyridoxine, folic acid.
- Correction of anemia by blood transfusion.

Q. What is **ring sideroblast**?

A. It is characterized by accumulation of iron in mitochondria of erythroblast around the nucleus, giving a ring shaped appearance in the bone marrow.

CHAPTER 11

Dermatology

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EXFOLIATIVE DERMATITIS OR ERYTHRODERMA

CHIEF COMPLAINTS

- Generalized scaling and redness for … months
- Pruritus all over the body for … months
- Chill and shivering for … days.

HISTORY

History of present illness: The patient states that he was reasonably well … months back. Since then, he has been suffering from recurrent pruritic lesions on the back of elbows, front of knees, extensor surfaces of extremities and lower back. Later on, the scalp and nails were involved. The lesions were elevated, circular, reddish and scaly. The scales were silvery white in color. He noticed bleeding after scratching of the lesions. The patient also noticed appearance of new lesions on scratch marks. These lesions are not associated with exposure to any allergen or food or exposure to sun. This type of attack occurred several times over the last … months.

For the last … months, the patient noticed generalized scaling and redness almost all over the body that is associated with extreme weakness, itching and loss of appetite. This is associated with chill and also occasional shivering for … days. He mentioned that following use of some topical medicine prescribed by a physician, there was some improvement. But there is recurrence of the same lesions after few days. His bowel and bladder habits are normal. There is no history of fever, arthralgia or arthritis, mouth ulcer, etc.

History of past illness: The patient did not suffer from any serious illness in the past.

Family history: There is no history of similar illness in the family. All the members of the family are in good health.

Personal history: He is married and has a son. He smokes 3 to 4 sticks/day for the last 10 years, but nonalcoholic. There is extramarital sexual exposure 3 years back.

Drug and treatment history: He was treated by local physicians with several antibiotics, systemic and topical steroid, antifungal agents, etc.

Socioeconomic condition: He is a businessman and comes from a middle class family. He lives in a semi pakka house with good sanitation and water supply.

GENERAL EXAMINATION

- The patient looks ill and emaciated with poor nutrition
- Mildly anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia, edema
- Few lymph nodes are palpable in cervical region that are discrete, soft in consistency and nontender
- No thyromegaly
- Pulse: 110/min
- Blood pressure: 110/70 mm of Hg
- Respiratory rate: 16/min
- Temperature: 98ºF.

SYSTEMIC EXAMINATION

Integumentary System

- Skin: Generalized exfoliation and erythema covering all over the body. Scales are white in color. Desquamation occurs in sheets from palms and soles. Skin is warm and dry. There is no tenderness.
- Hair: Color and texture of scalp hair is normal. Body hair is sparse.
- Nail: Brittle, yellow, dystrophic with subungual hyperkeratosis and distal onycholysis, nail folds are separated. Beau's line is present in some of the nails.
- Oral mucosa: Normal.
- Conjunctiva: Normal.
- Genitalia: Normal.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURE

Mr …, 35 years old, businessman, normotensive, nondiabetic, hailing from … presented with recurrent pruritic lesions on the back of elbows, front of knees, extensor surfaces of extremities and lower back for … months. Later on, the scalp and nails were involved. The lesions were elevated, circular, reddish and scaly. The scales were silvery white in color. He noticed bleeding after scratching of the lesions. The patient also noticed appearance of new lesions on scratch marks. These lesions are not associated with exposure to any allergen or food or exposure to sun. This type of attack occurred several times over the last … years.

For the last … months, the patient noticed generalized scaling and redness almost all over the body that is associated with extreme weakness, itching and loss of appetite. This is associated with chill and also occasional shivering for … days. He mentioned that following use of some topical medicine prescribed by a physician, there was some improvement. But there is recurrence of the same lesions after few days. His bowel and bladder habits are normal. There is no history of fever, arthralgia or arthritis, mouth ulcer, etc. There is no significant family history. He is nonalcoholic but smokes 3 to 4 sticks/day for the last 10 years.

On general examination – mention as above

On examination of integumentary system, there was generalized exfoliation and erythema covering almost all over the body. Skin is dry and warm. Koebner's phenomenon was observed. Nails are brittle, yellowish with subungual hyperkeratosis, onycholysis and dystrophy.

Examination of the other systems reveals no abnormalities.

My diagnosis is exfoliative dermatitis due to psoriasis.

Q. Why your diagnosis is exfoliative dermatitis due to psoriasis?

A. Because, there is history of scaly plaque type lesions on the elbow, knee, sacrum, scalp and extensor surface of the extremities. Scales are silvery white in color. Koebner's phenomenon is positive. All are suggestive of psoriasis.

Q. What are your **differential diagnoses?**

A. As follows:

- Exfoliative dermatitis because of drugs
- Exfoliative dermatitis because of Pityriasis rubra pilaris
- Exfoliative dermatitis because of Pemphigus foliaceous.

Q. What are the **points in favor and against** your differential diagnoses?

A. As follows:

Differential diagnoses	Points in favor	Points against
1. Exfoliative dermatitis because of drugs	Generalized exfoliation	No history of taking drugs that usually causes erythroderma Long history with recurrence and remission
2. Exfoliative dermatitis because of pityriasis rubra pilaris	Generalized exfoliation Involvement of palms and soles	Age is not suggestive No follicular papules, islands of normal skin or appearance of exaggerated goose flesh
3. Exfoliative dermatitis because of pemphigus foliaceus	Generalized exfoliation	No history of bullae Sites and nature of the previous skin lesions are not suggestive

Q. What **investigations** do you suggest in your case?

A. As follows:

1. Routine investigations:
   - Complete blood count and PBF (there may be normochromic normocytic anemia, leukocytosis, eosinophilia, high ESR, immature cells in leukemia).
   - Chest X-ray P/A view (to see complication like pneumonia, in suspected cases of lymphoma, sarcoidosis, etc.).
   - Urine R/M/E (to see proteinuria).
   - Total protein, albumin and globulin ratio (hypoproteinemia, altered A:G ratio).
   - Serum electrolytes (hypokalemia, hyponatremia, hypochloremia).
   - Blood urea and serum creatinine.
   - Serum uric acid level.
   - Serum IgE (elevated in some cases, especially in cases of atopic dermatitis).
2. Definitive diagnosis by skin biopsy for histopathology:
   - Histopathological findings help to identify the cause of erythroderma in up to 50% cases, particularly if multiple skin biopsies are examined. In psoriasis, papillomatosis and clubbing of the papillary zones may be seen. In pemphigus, superficial acantholysis will be present. In ichthyosiform erythroderma and pityriasis rubra pilaris, repeated biopsy from carefully selected sites may reveal their characteristic features.
   - Direct immunofluorescence test should be done to see immunoglobulin deposits in pemphigus foliaceus or lichen planus, etc.
3. Others to exclude primary cause:
   - Skin scraping for fungus and fungal culture in suspected cases of dermatophytosis
   - HIV cases (Anti HIV I and II, Western blot)
   - Ultrasonogram of the whole abdomen (to exclude malignancy or to see hepatomegaly and splenomegaly)
   - Bone marrow examination (to exclude leukemia)
   - CT and MRI (in some cases).

Q. How to **treat** the case?

A. As follows:

1. **General measures:**
   - Maintenance of fluid balance (intake and output monitoring)
   - Maintenance of electrolyte balance

- Good nutrition and protein balance by high protein diet
- Maintenance of environmental temperature
- Frequent bathing.

2. **Topical treatment:**
   - Lubricant and emollient (e.g. liquid paraffin)—apply two times daily
   - Mild topical steroid ointment (hydrocortisone)—apply once daily.
3. **Symptomatic treatment:**
   - Antihistamine (e.g. cetirizine, loratidine)
   - Antibiotic, if secondary infection is suspected
   - Iron, vitamin, folic acid supplement.
4. **Specific systemic treatment:**
   - Psoriatic erythroderma—Methotrexate (7.5 to 10 mg in single or 2 divided doses weekly). Other drugs—cyclosporine, acitretin, etc. may be given.
   - Isotretinoin may be used in pityriasis rubra pilaris.
   - PUVA therapy can be used in mycosis fungoides or psoriasis.
   - Immunosuppressives, such as azathioprine, cyclophosphamide may be required occasionally.
5. **Treatment of primary causes,** such as specific therapy for lymphoma and leukemias.

Q. What are the different **emollients and lubricants** that can be used in erythroderma?

A. Liquid paraffin, Vaseline, olive oil or lac hydrin (12% ammonium lactate) can be used as emollients.

Q. What are the **new drugs** that are used in psoriasis?

A. New drugs that are being used in psoriasis are tacrolimus, mycophenolate mofetil, hydroxyurea, 6 thioguanine and biologic agents, such as infliximab, etanercept, alefacept.

Q. What is the role of **systemic steroid in erythroderma?**

A. Systemic steroid should be avoided if possible, because of the dangers of fluid retention, secondary infection, diabetes and other complications. Steroid is also avoided in psoriatic erythroderma, because it may provoke the development of pustular psoriasis.

However, it may be used cautiously in atopic and seborrheic dermatitis. Only in severe persistent cases, systemic steroid is given. In that case, triamcinolone acetonide 80 mg is injected intramuscularly as initial dose. It can be repeated in 4th, 7th and 10th day, according to the condition of the patient.

RELATED QUESTIONS AND ANSWERS

Q. What are the **causes** of exfoliative dermatitis?

A. As follows:

1. Primary or Idiopathic.
2. Secondary to:
   - Cutaneous disease—psoriasis, atopic dermatitis, contact dermatitis, dermatophytosis, dermatomyositis, Hailey-Hailey disease, ichthyosiform erythroderma, Leiner's disease, lichen planus, SLE, mastocytosis, mycosis fungoides, Norwegian scabies, pemphigoid, pemphigus foliaceus, pityriasis rubra pilaris, Reiter's syndrome, sarcoidosis, seborrheic dermatitis, stasis dermatitis.
   - Systemic disease or malignancy—acute and chronic leukemia, lymphoma, carcinoma of the lung, rectum, fallopian tubes, multiple myeloma, mycosis fungoides, HIV infection, graft versus host disease.
   - Drugs—allopurinol, carbamazepine, sulfonamide, aminoglycosides, arsenic, aspirin, barbiturates, calcium channel blocker, captopril, cephalosporin, chlorpromazine, dapsone,

diltiazem, isoniazid, lithium, minocycline, neomycin, nalidixic acid, penicillin, phenothiazines, ranitidine, rifampicin, streptomycin, sulfonylurea, thiazides, trimethoprim, vancomycin.

Q. What are the causes of **Koebner's phenemenon?**

A. The following diseases show Koebner's phenomenon:

- Psoriasis
- Lichen planus
- Viral wart (verruca plana)
- Pityriasis rubra pilaris
- Nummular eczema
- Infectious eczematoid dermatitis
- Molluscum contagiosum
- Darier's disease
- Vitiligo
- Keratoacanthoma
- Reactive perforating collagenosis
- Erythema multiformi.

Q. What are the causes of **psoriasiform lesions?**

A. Causes of psoriasiform lesions are:

- Psoriasis
- Seborrheic dermatitis
- Pityriasis rubra pilaris
- Pityriasis rosea
- Parapsoriasis
- Subacute cutaneous lupus erythematosus
- Secondary syphilis
- Premycotic stage of mycosis fungoides.

Q. What are the causes of **erythroderma in adults?**

A. As follows:

- Idiopathic
- Psoriasis
- Atopic dermatitis
- Neurodermatitis
- Drug allergy
- Lymphoma
- Leukemia
- Contact dermatitis
- Seborrheic dermatitis
- Stasis dermatitis
- Pityriasis rubra pilaris
- Pemphigus foliaceus.

Q. What are the causes of **erythroderma in childhood?**

A. As follows:

- Atopic dermatitis
- Drugs
- Leukemia
- Childhood dermatomyositis
- Bullous ichthyosiform erythroderma

- Non-bullous ichthyosiform erythroderma
- Lamellar ichthyosis
- Pityriasis rubra pilaris
- Idiopathic
- Generalized dermatophytosis
- Leiner's disease.

Q. How a patient **presents** with exfoliative dermatitis?

A. The patient presents with:

- Generalized scaling
- Widespread erythema
- Dehydration or edema.

> **Note Remember the following:**
>
> Males are affected 2 to 3 times more frequently than females.

Q. What are the **clinical features** of exfoliative dermatitis?

A. Clinical features are is similar in most patients and characterized by:

1. Cutaneous manifestations:
   - Universal or extensive scaling covering more than 90% of the body surface
   - Pruritus and widespread erythema
   - Skin thickening
   - Loss of hair (often)
   - Nails may be dystrophic
   - Palms and soles are involved
   - Mucous membranes are usually spared although mucous membrane of the upper respiratory tract and conjunctiva (ectropion) may be involved.
2. Systemic manifestations:
   - Diarrhea
   - Anemia
   - Edema
   - Tachycardia
   - Lymphadenopathy (due to reactive hyperplasia)
   - Hepatomegaly (in 7% to 37% of the cases)
   - Splenomegaly (in 3% to 23% of the cases)
   - Occasionally, gynecomastia.

Q. What is the **pathogenesis** of psoriasis?

A. There is increase in the rate of epidermal turnover. The number of germinative cells and their absolute mitotic rate is increased. Transit time of the cells through the epidermis is shortened. Consequently, more material is lost from the epidermis. The desquamated cells show increased amount of nucleic acids and their degenerative products, decreased amount of free amino acids and increased amount of soluble protein.

Q. What **skin dysfunctions** occur in exfoliative dermatitis?

A. As follows:

- Loss of permeability barrier
- Marked scaling

- Marked vasopermeability
- Marked vasodilatation.

Q. What are the **complications** of exfoliative dermatitis?

A. There are multiple metabolic and systemic complications, such as:
- Secondary bacterial infection (cutaneous, subcutaneous and respiratory)
- Fluid loss, dehydration and electrolyte imbalance
- Protein loss (hypoalbuminema), leading to edema
- Xerosis
- Hypothermia
- High output cardiac failure
- Dermatogenic enteropathy
- Thrombophlebitis.

Q. What are the other causes of **dermatogenic enteropathy (diarrhea)?**

A. As follows:
- Dermatitis herpetiformis
- Pellagra
- Acrodermatitis enteropathica
- Candidiasis
- HIV.

Q. What are the causes of **ectropion?**

A. Causes of ectropion are:
- Exfoliative dermatitis
- Lamellar ichthyosis
- Non-bullous ichthyosiform erythroderma
- Sezary syndrome
- Lepromatous leprosy
- Lupus vulgaris
- Congenital eryhropoietic porphyria.

Q. What are the causes of **exfoliative dermatitis with nail changes?**

A. As follows:
- Psoriasis
- Pityriasis rubra pilaris
- Lichen planus
- Dermatophytosis
- Atopic dermatitis.

Q. What are the **bullous diseases causing exfoliative dermatitis?**

A. As follows:
- Congenital bullous ichthyosiform erythroderma
- Bullous pemphigoid
- Pemphigus foliaceus
- Hailey Hailey disease.

Q. Why **hypoproteinemia** occurs in exfoliative dermatitis?

A. As follows:
- Increased protein loss through scaling or leaking through the skin
- Protein loosing enteropathy

- Decreased synthesis and increased catabolism of protein
- Dilution by increased plasma volume.

Q. What are the **histopathological findings of psoriasis?**

A. Histopathology in psoriasis shows:

- Hyperkeratosis and parakeratosis (parakeratosis is more prominent, characterized by immature cells in stratum corneum).
- Presence of neutrophilic microabcess (Munro's) in the stratum corneum.
- Granular layer is thin or absent over the tips of dilated dermal papilla.
- Acanthosis (hyperplasia of the stratum malpighii) with test tube like elongation of rete ridges.
- Spongiform pustule in the spinous layer.
- Dilated and tortuous blood vessels in dermal papillae.
- Perivascular mononuclear cell infiltrate.

Q. What are the **prognoses** of exfoliative dermatitis?

A. As follows:

- Prognosis is good in drug induced cases after the offending drug is withdrawn
- Prognosis is poor in cases of idiopathic erythroderma
- Frequent recurrences or chronic symptoms require long-term steroid therapy and its sequelae
- In patient with the underlying disease or malignancy, prognosis depends on the primary cause
- The mean duration of the disease is 5 years with a median of 10 months
- Mortality rate is 20 to 40%
- Cause of death is unrelated to erythroderma in 20%.

PSORIASIS

CHIEF COMPLAINTS

- Multiple erythematous lesions with silvery white scales on different sites of the body for … years
- Occasional itching for … months.

HISTORY

History of present illness: The patient states that he was reasonably well … years back. Since then, he has been suffering from multiple reddish, scaly lesions of different shapes and sizes on scalp, front of knees, back of elbows, over the sacrum and extensor surfaces of the extremities. The scales are dry, white, thick and in some places large sheet-like. There is no oozing or discharge, but there is occasional itching. He noticed bleeding upon scratching of the lesions and appearance of new lesions on the scratch marks. In the scalp, the lesions does not causes fall of hair. He was treated with some topical emollients and antihistamine as prescribed by local doctors with some benefits. But the lesions recurred after some days and he had several attacks over the last … years. The lesions are gradually increasing,

These lesions are not associated with exposure to any allergen or food or exposure to sunlight. He did not take any drugs prior to this illness. There is no history of joint pain, photosensitivity, atopy, cough, chest pain, shortness of breath, jaundice, diarrhea, urethral discharge, eye changes, mouth ulcer, proximal muscular pain or weakness. He denies any extramarital exposure. His bowel and bladder habits are normal.

History of past illness

Family history: His father suffered from similar scaly skin disease.

Personal history

Drug and treatment history

Socioeconomic condition: Mention according to the patient's statement.

GENERAL EXAMINATION

- Mildly anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia, edema
- No lymphadenopathy or thyromegaly
- Pulse: 100/min
- Blood pressure: 110/70 mm of Hg
- Respiratory rate: 16/min
- Temperature: 98ºF.

SYSTEMIC EXAMINATION

Integumentary System

- Skin: There are multiple, well defined, erythematous, scaly plaques with silvery white scales involving scalp, elbows, knees, sacrum and extensor surfaces of the body. Auspitz sign is positive. Koebner phenomenon is positive.

- Hair: Normal.
- Nail: Subungual hyperkeratosis, nail pitting, oil drop sign positive.
- Mucous membrane:
  - Mouth—normal
  - Conjunctiva—normal
  - Genitalia—normal.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURE

Mr …, 35 years old, businessman, normotensive, nondiabetic, hailing from …, presented with multiple elevated, circular, reddish, scaly lesions of different shapes and sizes on scalp, front of knees, back of elbows, over the sacrum and extensor surfaces of the extremities for … years. The scales are dry, silvery white, thick and in some places large sheet-like. There is no oozing or discharge, but there is occasional itching. He noticed bleeding upon scratching of the lesions and appearance of new lesions on the scratch marks. In the scalp, the lesions do not cause fall of hair. He was treated with some topical emollients and antihistamine as prescribed by local doctors with some benefits. But the lesions recurred after some days and he had several attacks over the last … years. The lesions are gradually increasing, not associated with exposure to any allergen or food or exposure to sunlight. He did not take any drugs prior to this illness. There is no history of joint pain, photosensitivity, atopy, cough, chest pain, shortness of breath, jaundice, diarrhea, urethral discharge, eye changes, mouth ulcer, proximal muscular pain or weakness. He denies any extramarital exposure. His bowel and bladder habits are normal. His father suffered from similar scaly skin disease. There is no family history of similar illness. He was treated with several creams and ointments and antihistamine tablets by local physicians.

General examination (as above).

Examination of integumentary system (as above).

Examination of the other systems reveals no abnormalities.

My diagnosis is psoriasis (plaque type).

Q. Why do you think this is a case of psoriasis?

A. Because the patient gives a long history of skin lesions, mostly on extensor surface, with relapse and remission and occasional itching. On examination, there are well-defined erythematous scaly plaques with silvery white scale involving scalp, elbows, knees, sacrum and extensor surfaces of the body with positive Auspitz sign and Koebner phenomenon. There is also subungual hyperkeratosis, nail pitting and oil drop sign on the nails. So my diagnosis is psoriasis.

Q. What are your **differential diagnoses**?

A. As follows (for details, see below):

- Pityriasis rubra pilaris
- Seborrheic dermatitis
- Lichen planus
- Pityriasis rosea
- Subacute cutaneous lupus erythematosus (SCLE)
- Parapsoriasis—large and small plaque
- Psoriasiform sarcoid
- Psoriasiform secondary syphilis

- Plaque stage of mycosis fungoides
- Dermatophytosis
- Dermatomyositis.

Q. What **investigations** should be done in psoriasis?

A. As follows:

1. Routine:
   - Complete blood count (CBC)
   - Liver function test (LFT)
   - Serum creatinine
   - Lipid profile
   - X-ray chest
   - Urine R/M/E (to see proteinuria)
   - Serum electrolytes (hypokalemia, hyponatremia, hypochloremia)
   - Serum uric acid level
   - Serum IgE (to differentiate from atopic dermatitis).
2. To establish the diagnosis, the following procedures may be performed:
   - Skin biopsy for histopathology (definitive)
   - Antistreptolysin O (ASO) titer (high in guttate psoriasis)
   - Throat swab culture and sensitivity (in guttate psoriasis)
   - X-ray of the affected joints (to see psoriatic arthritis).
3. To exclude other causes, the following tests may be performed:
   - VDRL, TPHA, anti-nuclear antibody (ANA), anti SS-A, anti SS-B, direct immunofluorescence (DIF) and skin scraping for fungus.

Q. What are the **histological findings?**

A. As follows:

- Hyperkeratosis, parakeratosis, orthokeratosis
- Neutrophilic microabscess of Munro in the stratum corneum
- Granular layer is absent or thin over the dermal papilla
- Spongiform pustule of Kogoj in stratum spinosum
- Regular elongation of rete ridges that are club shaped
- Dermal capillary dilatation and tortuosity surrounded by a mixed neutrophilic and lymphohistiocytic perivascular infiltrate.

QUESTIONS RELATED TO PSORIASIS

Q. What are the **sites** of psoriatic skin lesion?

A. Extensor surfaces of knee, elbow, wrist, back of ear, scalp, hairline, extensor of limbs, sacrum, around the umbilicus, intergluteal cleft and flexures (natal cleft, axillary fold) and submammary fold.

Q. What **areas** have you examined other than skin to diagnose psoriasis?

A. As follows:

- Nails—pitting, oil spot, cracking of free edges, onycholysis (separation of nail plate from its bed), thickening and subungual hyperkeratosis
- Joints—arthropathy
- Eye—iritis (may be blepharitis, keratitis and conjunctivitis)
- (Tongue—geographical tongue may be associated).

Q. What are your **differential diagnoses**?

A. As follows:

- Pityriasis rubra pilaris (sandle-like palmo-plantar keratoderma, islands of normal skin, follicular papules).
- Seborrheic dermatitis (greasy, yellowish scale on eyebrows, nasolabial crease, gluteal crease, ears, sternal region, axilla, submammary folds, umbilicus and groin).
- Lichen planus (usually on flexor surface, Wickham striae, violaceous flat-topped papules and adherent scale, white violaceous lacy patch on buccal mucosa).
- Pityriasis rosea (short duration, herald patch and collarette scaling on trunk, upper arms and thighs).
- Subacute cutaneous lupus erythematosus (SCLE) (female sex, photosensitivity, photodistributed area and over back).
- Parapsoriasis (large and small plaque, long duration, asymptomatic, fine scale, truncal involvement, patches of variable size).
- Psoriasiform sarcoid (truncal involvement, no nail change, systemic symptoms of sarcoidosis, such as fever, cough, breathlessness on exertion, joint pain).
- Psoriasiform secondary syphilis (history of extramarital exposure, duration is less than 3 months, history of chancre on genitalia, generalized lymphadenopathy, condyloma lata, mucous patches on oral cavity).
- Plaque stage of mycosis fungoides (middle aged patient, severely pruritic).
- Dermatophytosis (tinea corporis, cruris and pedis. There is itching, scaly patch active papulo-vesicular border and central clearing).
- Dermatomyositis (heliotrope sign, atrophy and poikiloderma, muscular weakness).

Q. What is **mycosis fungoides**?

A. Mycosis fungoides (cutaneous T cell lymphoma) is a rare skin tumor that develops slowly over many years (sometimes 20 to 30 years). It is characterized by reddish-brown, scaly and itchy plaques that, in early stages, resemble erythematous lesions of psoriasis or eczema. There may be enlargement of lymph nodes. Occasionally, it can progress to a cutaneous nodular or tumor stage. In elderly male, the disease may progress rarely to an erythrodermic variant accompanied by lymphadenopathy and peripheral blood involvement (Sezary syndrome).

Skin biopsy confirms the diagnosis.

Early cutaneous disease can be left untreated or treated with topical steroid or PUVA. In advanced cases, radiotherapy, chemotherapy (e.g. methotrexate), immunotherapy or electron beam therapy may be used.

Q. What is **Sezary's syndrome**?

A. Sezary's syndrome is erythrodermic variant of mycosis fungoides (cutaneous T cell lymphoma), characterized by erythroderma, lymphadenopathy and large mononuclear cells (Sezary cells) in the skin and blood. It is often resistant to treatment and carries poor prognosis.

Q. What is **Auspitz's sign** and **Koebner's phenomenon** in psoriasis?

A. As follows:

- Auspitz's sign: When the silvery scales are plucked, capillary bleeding occurs.
- Koebner's phenomenon: New psoriatic lesion is produced when the normal skin of a psoriatic patient is scratched or injured (may occur in surgical scar).

Note Remember the following:

There is moist red surface on removal of the scales called Bulkeley's sign.

Q. What is **Koebner's phenomenon**? What are the **causes** of Koebner's phenomenon?

A. Koebner's phenomenon is the appearance of isomorphic skin lesions at the site of trauma, burn or scratch mark in normal skin. Causes are:

- Psoriasis
- Lichen planus
- Warts (verruca plana)
- Others—vitiligo, pityriasis rubra pilaris, molluscum contagiosum, nummular eczema and Darier's disease.

Q. What are the factors that **aggravate** psoriasis?

A. The aggravating factors are:

1. Trauma
2. Infections—β-hemolytic streptococci (aggravates guttate psoriasis) and HIV infection
3. Psychological factors—emotion and anxiety
4. Drugs:
   - β-Blockers
   - Antimalarial (chloroquine and hydroxychloroquine)
   - Lithium
   - Alcohol
   - Angiotensin-converting enzyme (ACE) inhibitors
   - NSAIDs (e.g. indomethacin)
   - Systemic steroid—the disease is aggravated after withdrawal of steroid (rebound phenomenon) and also after stopping following prolonged use of local steroid
   - Terbinafine
   - Gemfibrozil
   - Glyburide
   - Granulocyte colony stimulating factor
   - Interleukins
   - Interferons
5. Rarely, sunlight (UVR may worsen)
6. Metabolic (hypocalcemia and dialysis).

Q. What is **psoriasis**? What are the various **types** of psoriasis?

A. It is a chronic inflammatory disease of skin characterized by well-defined erythematous plaque with silvery white scales, involving commonly the extensor surface, elbows, knees and sacral regions associated with recurrence and remission. It affects 1 to 2% of the population.

There are four types:

- Chronic plaque psoriasis (Common. Well demarcated, red with a dry silvery white scale. It commonly involves elbow, knee and lower back, but may also involve scalp, nails, flexures, palms).
- Guttate psoriasis (Raindrop-like psoriasis is a variant, common in children and young adults. An explosive eruption of very small circular or oval plaques appears over the trunk about 2 weeks after a streptococcal sore throat. Majority of the patients develop plaque psoriasis in later life).
- Pustular psoriasis (It may be localized involving palm and sole or rarely generalized that may be serious).
- Erythrodermic psoriasis (> 90% of body surface area becomes red and scaly).

Q. What are the **clinical patterns** of psoriasis?

A. According to some authorities, psoriasis is of the following types:

1. Psoriasis vulgaris, chronic stationary psoriasis, plaque type psoriasis

2. Guttate (eruptive) psoriasis
3. Small plaque psoriasis
4. Inverse psoriasis
5. Erythrodermic psoriasis
6. Pustular psoriasis:
   - Generalized pustular psoriasis of von Zumbusch
   - Exanthematic pustular psoriasis
   - Annular pustular psoriasis
   - Localized pustular psoriasis
7. Atypical forms:
   - Linear and zonal lesions
   - Sebopsoriasis
   - Mucosal lesions (rare but has been associated with cutaneous)
   - Ocular lesions—blepharitis, conjunctivitis, keratitis.

Q. What is the **pathology** of psoriasis?

A. Rapid proliferation and abnormal differentiation of epidermis (because of hyperproliferation of keratinocyte) and infiltration of inflammatory cells (polymorph, T-lymphocyte and other inflammatory cells). Accelerated epidermopoiesis is considered to be the fundamental pathological event in psoriasis.

Q. What are the **types of arthritis** in psoriasis?

A. There are 5 clinical patterns of arthritis in psoriasis:

- Asymmetrical DIP joint involvement with nail damage
- Symmetrical polyarthritis, such as rheumatoid arthritis with claw hands
- Asymmetrical oligoarthritis with swelling and tenosynovitis of one or a few hand joints
- Ankylosing spondylitis alone or with peripheral arthritis
- Arthritis mutilans with osteolysis of phalanges and metacarpals.

Q. What are the **complications** of psoriasis?

A. As follows:

- Psoriatic arthropathy
- Exfoliative dermatitis
- Secondary infection
- Hyperuricemia and gout
- Others—amyloidosis, renal failure, hepatic failure and high output cardiac failure because of erythroderma.

Q. How to assess the **severity** of psoriasis?

A. As follows:

- Patient's own perception of disability
- Objective assessment of disability—usually estimated by using the Psoriasis Area and Severity Index (PASI). The areas of involvement, erythema, induration, desquamation (EID) are considered. Maximal score on this index is 72 with mild, moderate and severe having scores of <10, 10 to 50 and > 50 respectively.

Q. Name the drugs that will help to cure **both psoriasis and arthritis**.

A. Methotrexate, azathioprine and acitretin.

Q. How to **treat** psoriasis?

A. As follows:

1. General measures:
   - Explanation and reassurance
   - Avoid trauma, precipitating drugs and anxiety.
2. Specific treatment:
   - Local therapy
   - Systemic therapy
   - Combination therapy.

Local therapy (topical therapy on the lesion):

- Emollient—Lubricate and soothe dry, scaly and inflamed skin. It is helpful in reducing dryness, scaling, cracking, soreness and itching. Common emollients are petrolatum, paraffin, urea (up to 10%), olive oil, etc.
- Salicylic acid (≥ 5%)—It is keratolytic, used to soften and remove scale from psoriatic plaques. It is often combined with other topical medications to enhance their effectiveness (betamethasone dipropionate and salicylic acid). Widespread application may lead to salicylic toxicity, such as tinnitus, acute confusion and refractory hypoglycemia especially in patient with diabetes and compromised renal function.
- Crude tar (3 to 5%)—It inhibits DNA synthesis. Exact action is unknown but has antiproliferative and anti-inflammatory effect. Allergic reactions, folliculitis, carcinoma, offensive odor, staining of clothing are side effects.
- Dithranol (inhibits DNA synthesis).
- Calcipotriol—It is a vitamin D3 analog. It inhibits epidermal proliferation and restores normal horny layer. It is applied locally twice daily, very effective in the treatment of plaque type and scalp psoriasis. It may cause hypercalcemia and hypercalciuria. Combination therapy with calcipotriene and high potency steroids may provide greater response rates, fewer side effects and steroid sparing. Calcipotriene is unstable in the presence of many other topical agents and degrades in the presence of UV light.
- Tazarotene—3rd generation topical retinoid. It acts by modulating keratinocyte differentiation and hyperproliferation, also by suppressing inflammation. Combining its use with a topical corticosteroid and weekend pulse therapy can decrease irritation.
- Topical steroid (mildly potent to super potent according to severity of disease).
- UVR therapy—Narrow band UVB (peak emission around 311 nm) has been proved more effective than broadband UVB. However, it may cause burning. Patients are treated 3 to 5 times per week. On clearing, either treatment is discontinued or patients are subjected to maintenance therapy for 1 to 2 months. During this period, the frequency of UVB therapy is reduced while maintaining the last dose given at the time of clearing.
- Tacrolimus and pimecrolimus—Helpful for thin lesions in areas prone to atrophy or steroid acne. Burning sensation occurs with these agents, but may be avoided by prior treatment with corticosteroid, and by application to dry skin, rather than after bathing.
- Excimer laser—The monochromatic 308 nm excimer laser can deliver supra-erythemogenic doses of light focally to the lesional skin, given twice weekly. The role of this treatment seems to be indicated for patients with stable recalcitrant plaques particularly in the elbow and knee region.

Systemic therapy:

- PUVA (psoralen and UVA)—Long-term use may cause squamous cell carcinoma, basal cell carcinoma and melanoma.
- Retinoid (acitretin)—May help for arthritis and psoriasis (especially pustular and also plaque). Avoid in young female patients (it is teratogenic).
- Methotrexate.

- Azathioprine.
- Cyclosporine is given in patient with widespread, severe inflammatory or erythrodermic psoriasis, mainly if there is failure of other treatment and if the patient cannot tolerate other drugs. It is used as a rotational therapeutic option or as a first line treatment in generalized plaque type psoriasis.
  It acts by down modulation of proinflammatory epidermal cytokines (IL-2, IFN-γ). The dose is 2 to 5 mg/kg/day in adults and 5 to 7 mg/kg/day in children. It can be started with 2.5 mg/kg/day, increased every 2 to 4 weeks up to 5 mg/kg/day. Tapering is recommended on discontinuation. It is effective in up to 90% cases. Nephrotoxicity, hypertension, neurotoxicity and nonmelanoma skin cancers are the side effects. It is not teratogenic. It reduces the effectiveness of progestin based contraceptives.
- Biologic agents—Monoclonal antibody can produce dramatic response in some patients. These agents suppress the normal immune response. Commonly used drug is anti-tumor necrosis factor alpha (anti-TNF-α, such as infliximab, etanercept, adalimumab and efulizumab), and it may be given, when all other drugs fail. Other biologic agents are—alefacept, human interleukin-12/23 monoclonal antibody, etc.
- Other drugs—Tacrolimus, mycophenolate mofetil, hydroxyurea and thioguanine.

Combination therapy:
- MTX plus topical agent
- MTX plus retinoid
- Retinoid plus PUVA
- MTX plus infliximab.

Alternative therapies for psoriasis:
- Mycophenolate mofetil
- Sulfasalazine
- Paclitaxel
- Azathioprine
- Fumeric acid esters
- Climatotherapy
- Grenz ray therapy.

For nail disease:
- Systemic agents
- Topical retinoids
- Local triamcinolone injections
- Topical fluorouracil.

BRIEF DESCRIPTION ABOUT THE DRUGS IN PSORIASIS

Psoralen ultraviolet A (PUVA) therapy:

All types of psoriasis respond to PUVA, though the management of erythrodermic or generalized pustular psoriasis is more difficult.

Mechanism of action:
- Photoconjugation of Psoralens to DNA with subsequent suppression of mitosis, DNA synthesis and cell proliferation, expected to revert increased cell rates in psoriasis to normal.
- May act by affecting immune function through a direct phototoxic effect on lymphocytes in skin infiltrates.

8-Methoxypsoralen (8 MOP) (Oxsoralen) in a dosage of 0.6 mg/kg is administered orally 2 hours before UVA irradiation.

Some patients treated with PUVA are able to achieve long-term remission even without maintenance therapies.

Treatments are administered 2 to 3 times per week and after 20 to 30 treatments, nearly 90% of patients achieved marked improvement or clearing.

Side effects of PUVA:
- Nausea (develops shortly after methoxsalen is ingested)
- Burns
- Lentigines
- Nonmelanoma skin cancer (SCC, BCC)
- Malignant melanoma.

Bath PUVA consists of 15 to 20 minutes of whole body emersion in solution of 0.5 to 5.0 mg 8 MOP per liter of bath water.

This treatment is highly effective for psoriasis of palm and soles that is usually recalcitrant to treatment.

Methotrexate:

Indications:
- Psoriatic erythroderma
- Psoriatic arthritis
- Acute pustular psoriasis (von Zumbusch type)
- Widespread body surface involvement
- Localized pustular psoriasis, palmo-plantar psoriasis that impairs normal function and employment.

Mechanism of action:
- MTX was thought to act directly to inhibit epidermal hyperproliferation via inhibition of dihydrofolate reductase (DHFR).
- It is now thought that the inhibition of DHFR is not the main mechanism of anti-inflammatory action of MTX but rather the inhibition of an enzyme involved in purine metabolism [5 aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase].
- This leads to accumulation of extracellular adenosine that has potent anti-inflammatory activity particularly for neutrophils.
- Consistent with a DHFR independent mechanism of action, concomitant administration of folic acid (1 to 5 mg/kg) reduces certain side effects, such as nausea and megaloblastic anemia without diminishing the efficacy of anti-psoriatic treatment.

Dosage:
- Single weekly dose (or 3 divided doses over a 24-hour period)
- A test dose of 5 to 10 mg is given. CBC and liver function test are done 6 to 7 days later
- Dose is gradually increased (2.5 to 5 mg/week), to see the response
- Most patients respond at 10 to 15 mg/week, rarely up to 30 mg/week
- When there is maximum response, MTX is tapered by 2.5 mg/week to see the lowest possible dose that controls the disease
- If single dose exceeds 25 mg, oral absorption is unpredictable and subcutaneous injection is recommended
- Pediatric dose—0.2 to 0.4 mg/kg/wk or 10 mg/m^2/wk.

Adverse effects:
- Nausea, anorexia, vomiting, diarrhea
- Oral and cutaneous ulceration
- Alopecia
- Headache
- Fatigue
- Bone marrow suppression
- Miscarriage and birth defect
- Temporarily effect fertility in males
- Acute pneumonitis
- Hepatotoxicity.

Monitoring guideline:
1. Baseline monitoring:
   - History and physical examination
   - Identification of patients at increased risk for toxicity
   - Recording concomitant medications that may interact with MTX
   - CBC and platelet count
   - Liver function tests
   - Serologic test for hepatitis A, B, C antibodies
   - Renal function tests (BUN, creatinine)
   - HIV testing, if any risk.
2. Follow-up monitoring:
   - CBC, platelet count and LFTs—Every 1 to 2 weeks for 2 to 4 weeks, then 1 to 2 weeks after dose escalation and finally gradually decrease frequency of tests to every 3 to 4 months long-term.
   - Renal function tests (once or twice yearly).

Liver biopsy:
- After every 1.5 to 2.0 g total dose for low-risk patients
- After every 1.0 g total dose for higher-risk patients
- Every 6 months for patients with grade IIIA liver biopsy changes
- Some groups have recommended the use of aminoterminal type III procollagen peptide assay for screening of liver biopsy. But, this is not yet approved by FDA.

Acitretin:

Indications:
- Generalized pustular psoriasis
- Erythrodermic psoriasis
- Severe recalcitrant psoriasis
- Severe plaque type psoriasis.

Mechanism of action:
- Antiproliferative effect
- Anti-inflammatory effect.

Dose:
- 25 mg/day with a maintenance dose of 20 to 50 mg/day
- Pediaric dose is 0.25 mg/kg/day

- Acitretin induces clearance of psoriasis in a dose dependent fashion (higher starting doses appeared to clear psoriasis faster).

Adverse effects:
- Cheilitis
- Dry skin
- Hair loss
- Failure to develop normal nail plate
- Periungual pyogenic granuloma
- Hyperlipidemia (particularly triglyceridemia)
- Pseudotumor cerebri (headache)
- Osteoporosis
- Calcification of ligaments
- Skeletal hyperostosis.

Fertile women with severe psoriasis who take acitretin must follow two methods of contraception or abstinence and have monthly pregnancy test during therapy and for an additional 3 years after withdrawal of drug.

Monitoring guideline:
1. Baseline monitoring:
   - History and physical examination
   - Pregnancy test
   - CBC and platelet count
   - Liver function test
   - Lipid profile
   - Renal function test (creatinine, BUN)
   - Urine analysis (if patients have renal diseases, proteinuria, diabetes or hypertension)
   - Consider baseline X-rays of wrist, ankles, or thoracic spine, for long-term retinoid therapy.
2. Follow-up monitoring—Monthly for the first 3 to 6 months, then every 3 months:
   - History and physical examination
   - CBC with platelet counts
   - Liver function test (AST, ALT)
   - Lipid profile (TG, cholesterol)
   - Renal function test
   - Urine analysis
   - Pregnancy test.

Most patients relapse within 2 months after discontinuing acitretin.

Acitretin should be discontinued if liver dysfunction, hyperlipidemia or diffuse idiopathic hyperostosis occurs.

Topical corticosteroid:

Topical application of corticosteroids in creams, ointments, lotions, foams and sprays is the most frequently prescribed therapy for psoriasis. Therapy can be continued with pulse applications on weekends to reduce the incidence of local adverse effects. Low to mid-strength steroids are preferred in the intertriginous areas and on the face. Areas with thick keratotic scales should be hydrated and covered with occlusive dressing after giving potent or super potent steroid.

Mechanism of action:

- Potent anti-inflammatory effects by inhibiting the release of phospholipase A_2
- They reduce T-cell proliferation and induce T-cell apoptosis
- Several cytokines are directly affected by corticosteroids including IL-1, TNF-α, GM-CSF and IL-8.
- The antiproliferative effect is mediated by inhibition of DNA synthesis and mitosis.

Side effects:

- Epidermal atrophy, thinning
- Striae
- Steroid acne
- Miliaria
- Pyoderma
- Hypopigmentation, persistent erythema, telangiectasia, hypertrichosis
- Tachyphylaxis.

No more than 45 g/week of potent or 100 g/week of weak or moderately potent topical corticosteroid should be applied, if systemic absorption is to be avoided.

DARIER'S DISEASE OR KERATOSIS FOLLICULARIS

CHIEF COMPLAINTS

- Multiple hyperpigmented pruritic elevated lesions over the different parts of the body for … months.
- Pain over some of the lesions for … months.

HISTORY

History of present illness: The patient states that he was quite well … months back. Since then, he noticed multiple hyperpigmented, rough, elevated lesions with mild pruritus over the scalp and nose. Gradually there is involvement of the forehead, face, ears, retro-auricular region, front of the chest, dorsum of both hands, back, lower legs and feet. Initially the lesions were relatively small, but gradually increased in size and extent, larger lesions involved the legs. Most of the lesions are covered with greasy crusts. The lesions are painful for the last … months. The pain is dull in nature that increases in intensity by touch or movement. He noticed occasional bleeding from the lesions on the lower part of the legs. There is no history of weight loss, anorexia, fever and joint pain. His bowel and bladder habits are normal.

History of past illness: The patient suffered from eczema on hands … years back. No other serious illness.

Drug history: He was treated by local physicians with azithromycin, doxycycline, aspirin, prednisolone, triamcinolone injection, etc. but there was no significant improvement.

Family history: His parents and siblings are all in good health and there is no such illness in his family.

Personal history: He is a shop-keeper,, smoker, used to take 3 to 5 sticks per day for 10 years. There is no history of sexual exposure.

Socioeconomic condition: He comes from a poor family with a monthly income of about 2000 Rs. He lives in a small house with poor sanitation and water supply.

GENERAL EXAMINATION

- The patient is ill looking and emaciated
- He is mildly anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia, edema
- There is no thyromegaly or lymphadenopathy
- Pulse: 72/min
- Blood pressure: 130/80 mm of Hg
- Temperature: 98ºF
- Respiratory rate: 18/min.

Integumentary System

1. **Skin:**
   - **Inspection**—There are multiple dirty, warty, greasy, crusted, bilaterally symmetrical papules are present over face, scalp, ear, front of the chest, back of the hands, lower part of both legs and dorsum of both feet. Some of the lesions of lower legs fused to form vegetating growths that are malodorous, fissured and eroded. Purulent exudate is present in between some of the lesions.
   - **Palpation**—The lesions are rough and firm in consistency, mostly non-tender but few on the legs are tender. After removal of the crust, there is eroded surface with bleeding points. Palms and soles are uniformly thickened.
2. **Hair:** Scalp is covered by greasy crust and hair is sparse.
3. **Nails:** Fragile with subungual hyperkeratosis, splintering, triangular nicking and alternate white and red streaks.
4. **Mucous membrane:**
   - Conjunctiva—normal
   - Oral mucosa—small white papules (cobble stone papules) on the palate
   - Genitalia—normal.

Examination of other systems reveals no abnormalities.

SALIENT FEATURE

Mr …, 25 years, shopkeeper, normotensive, nondiabetic, smoker, hailing from …, presented with the complaints of multiple hyperpigmented, dirty, warty, greasy, crusted papules and pruritus for … months. The lesions appeared first on forehead and nose and then gradually involved other parts, such as scalp, ear, front of the chest and limbs. These gradually increased in size and extent. He also complains of pain in some of the lesions for … months. The lesions on the lower part of the legs are larger, painful, malodourous and bleed occasionally. For this illness, he took azithromycin, aspirin, doxycycline, prednisolone, triamcinolone, etc. as advised by local physicians but there was no significant improvement. He had suffered from eczema … years back. There is no such illness in the family. He smokes 3 sticks of cigarette a day for the last 10 years.

On general examination – describe as above.

Examination of integumentary system – describe as above.

Examination of other systems reveals no abnormalities.

My diagnosis is Darier's disease.

Q. What are your **differential diagnoses?**

A. As follows:

- Arsenicosis
- Seborrheic folliculitis
- Pityriasis rubra pilaris
- Kyrle's disease.

Q. What are the **points in favor** and **against**?

A. As follows:

Differential diagnoses	Points in favor	Points against
1. Arsenicosis	» Drinks tubewell water » Keratotic papules present	» Punctate keratosis absent in palms and soles » No rain drop pigmentation » Face is affected severely
2. Seborrheic folliculitis	» Greasy papules present in seborrheic areas » Pruritus present	» Papules are dirty and warty » These are present in areas other than seborrheic areas, such as lower legs, palms, soles, nails and palate
3. Kyrle's disease	» Keratotic papules » Limbs, head, neck affected	» Dirty, warty, greasy crusted papule » Seborrheic area affected » Young age » Nondiabetic
4. Pityriasis rubra pilaris	» Follicular papules present » Plantar hyperkeratosis present	» Papules over the back of the fingers absent. » No nutmeg grater and islands of normal skin » Lesions are not papillosquamous

Q. What **investigations** should be done in this case?

A. As follows:

1. Routine:
   - Complete blood count
   - Blood sugar
   - Stool R/M/E
   - Urine R/M/E
   - Chest X-ray P/A view
   - Bleeding time, clotting time
   - Hair arsenic level (to exclude arsenicosis)
   - Others—Lipid profile (before starting retinoids), ECG, USG of whole abdomen
2. To confirm diagnosis—skin biopsy for histopathology.

RELATED QUESTIONS AND ANSWERS

Q. How to **treat?**

A. As follows:

A. Local treatment:
   - Dressing of the ulcerated lesions
   - Mupirocin ointment
   - Isotretinoin cream.

B. Systemic treatment:
   - Acitretin 10 mg daily
   - If infection, antibiotic should be given
   - Iron, vitamin and mineral may be used.

Q. What is **Darier's** disease?

A. Darier's disease is a genodermatosis, inherited as autosomal dominant with high penetrance (95%). New mutations are common. It does not manifest at birth, but majority is seen before 30 years. Males and females are affected equally. Prevalence is from 1 in 50,000 to 1 in 100,000.

Q. What are the diseases that show **disorders of keratinization?**

A. Diseases due to disorders of keratinization are:

- Darier's disease
- Congenital and acquired ichthyosis
- Pityriasis rotunda
- Porokeratosis
- Acrokeratosis verruciformis
- Palmoplantar keratoderma
- Knuckle pads.

Q. What are the **sites of involvement** of Darier's disease? How does it **manifest?**

A. As follows:

1. Seborrheic area: Face, scalp, forehead, nasolabial furrows, retroauricular region, lip, front of the chest, back, axilla, anogenital region, natal cleft. In these areas, the disease is manifested by dirty, warty, greasy, crusted papules that are usually symmetrical and widespread. As the lesions grow older, they fuse to form malodorous papillomatous and vegetating growths. These are eroded, fissured and covered by purulent exudate. There may be pain, pruritus and bleeding from the lesions and photokoebner.
2. Sites without sebaceous glands: Palms and soles. In these sites, features may be:
   - Uniform horny thickening
   - Punctate or filiform keratosis
   - Minutes pits (pathognomonic)
   - Dermatoglyphics will be normal.
3. Mucous membrane: White cobblestone papules may be seen on the palate, tongue, buccal mucosa, epiglottis. Pharyngeal wall, esophagus, rectum, larynx and vulva may also be involved. Confluence of the papules may simulate leukoplakia.
4. Nails: Show subungual hyperkeratosis, fragility, splintering with longitudinal alternating white and red streaks. Triangular nicking of the free edges will also be present.
5. There can be blockage of external auditory meatus and salivary glands also. Cornea may be affected rarely.

Q. What are the **types** of Darier's disease?

A. Four types:

1. Classical or seborrheic
2. Unilateral or zosteriform
3. Hypertrophic-in flexure like axilla, groin
4. Vesico bullous form.

Q. What are the diseases with **seborrheic presentation?**

A. As follows:

- Seborrheic dermatitis
- Darier's disease
- Seborrheic keratosis
- Letterer Siwe disease
- Pellagra
- Brazilian pemphigus.

Q. What are the diseases with **seasonal variations?**

A. As follows:

- Darier's disease—worse in summer
- Pellagra—worse in spring
- Eruptive keratoacanthoma—worse in summer
- Pityriasis rotunda—summer remission
- Hailey-Hailey disease—more protracted during summer.

Q. What are the **complications** of Darier's disease?

A. As follows:

- Herpes simplex infection
- Chronic pyogenic infection
- Kaposis varicelliform eruption
- Pox virus infection
- Defect in cell mediated immunity (complete anergy to skin test of delayed hypersensitivity). No abnormality to humoral immunity.

Q. What are the **differential diagnoses** of Darier's disease?

A. According to site of involvement, it may be confused with:

- Scalp—simulate seborrheic dermatitis
- Face—acne, seborrheic dermatitis
- Dorsum of hand, foot and shin—acrokeratosis verruciformis of Hopf, angiokeratoma, arsenicosis, follicular—pityriasis rubra pilaris, phrynoderma, keratosis pilaris, Kyrle's disease
- Trunk—arsenicosis, epidermodysplasia verruciformis
- Linear lesion—linear epidermal nevus
- Flexural—acanthosis nigricans, reticular papillomatosis, pemphigus vegetans.

Q. What are the **histopathological findings** of Darier's disease?

A. As follows:

- Hyperkeratosis, parakeratosis, acanthosis.
- Formation of suprabasal cleft lacuna via acantholysis with villi in the lacuna. In the lacuna, acantholytic dyskeratotic keratinocytes termed corps ronds and grains are present.
- Dermis shows chronic inflammatory infiltrate. Basal keratinocytes herniate into the dermis through the defect in the basal lamina.
- Vesicobullous lesion—lacuna are smaller in size. It contains numerous shrunken cells with appearance of grains.
- Mucosal lesion—similar but definite corps ronds and grains are usually absent.

Note Remember the following:

- Lacuna is formed by the changes in tonofilaments that become separated from desmosomes. Villi are the irregular upward proliferation into the lacuna of papilla lined by single layer of basal cells.
- Corps ronds are present mainly in the spinous layer. These are keratinocytes with a basophilic nucleus surrounded by a halo. Peripheral to the halo, basophilic dyskeratotic material lie as a shell. Due to the halo, they are conspicuous. These cells show premature partial keratinization.
- Grains are small dark cells with shrunken cytoplasm and pyknotic nucleus. They lie mostly in stratum corneum and as acantholytic cells in the lacuna.

Q. What are the **types of dyskeratosis?**

A. Two types:

1. Acantholytic dyskeratosis—occurs as corps ronds that are seen in:
   - Darier's disease
   - Warty dyskeratoma
   - Focal acantholytic dyskeratoma
   - Benign familial pemphigus.
2. Neoplastic dyskeratosis—also referred to as individual cell keratinization, manifests itself as homogeneous, eosinophilic bodies about 10 micron in diameter that occasionally show remnants of their nucleus. These may be seen in Bowen's disease, solar keratosis, squamous cell carcinoma, keratoacanthoma. It is not necessarily an indication of malignancy.

Q. What are the diseases **associated with Darier's disease?**

A. As follows:

- Retinitis pigmentosa
- Asymptomatic bone cyst
- Renal and testicular agenesis
- Autoimmune thyroid disease
- Epilepsy and encephalopathy.

Q. What are the modalities of **treatment** of Darier's disease?

A. As follows:

1. General measures:
   - Mild disease requires no treatment other than a simple emollient
   - The patient should be advised about the effects of sunshine.
2. Topical treatment:
   - Retinoids, such as tretinoin, 13-cis-retinoic acid, adalpene, tazarotene can be used.
3. Systemic treatment:
   - Isotretinoin, acitretin, cyclosporine can be used to control severe flares
   - Secondary infection with *Staphylococcus aureus* is responsible for some flares. In such case, antibiotic, such as cloxacillin, fluocloxacillin or cephalosporin should be given.
4. For hypertrophic lesions:
   - Dermabrasion
   - Laser excision
   - Excision and grafting

Q. What are the **characteristics** of **autosomal dominant** diseases? Name some autosomal diseases with dermatological manifestations.

A. Characteristics of autosomal dominant disease:

- It affects both male and female
- Affected individuals are heterozygous for the abnormal allele
- Every patient will have an affected parent apart from new mutations
- Half of the children of the affected parents will be affected
- Age of onset of the disease is variable. Affected person may remain symptom free up to adult life
- Severity of the disease will vary among the affected members of the family
- A few of the patients show lack of penetrance. These patients inherit the gene but do not show the disorder.

Autosomal dominant diseases with dermatological manifestations are:

- Neurofibromatosis

- Tuberous sclerosis
- Benign familial pemphigus
- Epidermolysis bullosa simplex
- Pseudoxanthoma elasticum
- Cutis laxa
- Darier's disease
- Acrokeratosis verruciformis of Hopf
- Pachyonychia congenita
- Monilethrix
- Peutz-Jeghers syndrome.

Q. What are the characteristics of **autosomal recessive** (AR) diseases? Name some AR disease with dermatological manifestation.

A. Characteristics of AR diseases are:

- It affects both male and female
- Affected individuals are homozygous for the abnormal allele
- Autosomal disorder occurs in a person whose healthy parents carry the same recessive gene
- Average 1 in 4 of children of heterozygous parents will be affected
- There is no family history although the defective gene may pass generation to generation
- It occurs within the group of brother and sister
- Consanguinity increases the risk of autosomal recessive disorders
- The offspring of the affected patient will be normal provided the other parent is normal
- The diseases are severe. Many of the autosomal recessive disorders are inborn error of metabolism.

Autosomal recessive diseases with dermatological manifestations are:

- Junctional epidermolysis bullosa
- Dystrophic epidermolysis bullosa, recessive form
- Werner's syndrome
- Harlequin fetus
- Lamellar ichthyosis
- Nonbullous ichthyosiform erythroderma
- Albinism
- Xeroderma pigmentosa
- Bloom syndrome
- Ataxia telangiectasia.

Q. What are the characteristics of **X-linked recessive** (XR) disorders? Name some XR diseases.

A. The characteristics of XR diseases are:

- Only males are affected
- The disorder is transmitted through healthy female carrier
- A female carrier will transmit the disease to half of her sons and half of her daughters will be the carrier
- When a male is affected, all his daughters will be the carrier
- This trait cannot be transmitted from father to son
- Frequently mother's brother will be affected
- X-linked disorders should be considered when family history indicates affected male in different generations
- Family history may not be always positive, as new mutations are common.

Some of the X-linked diseases are the following:

1. **Dermatological:**
   - Anhidrotic ectodermal dysplasia
   - X-linked ichthyosis
   - Ehler Danlos syndrome-type V
   - Ocular albinism
   - Menkes syndrome
   - Chronic granulomatous disease.
2. **Musculoskeletal:**
   - Duchenne muscular dystrophy.
3. **Blood:**
   - Hemophilia A and B
   - Glucose-6-phosphatase dehydrogenase deficiency.
4. **Immune:**
   - Agammaglobulinemia
   - Wiskott Aldrich syndrome.
5. **Metabolic:**
   - Diabetes insipidus.
6. **Nervous:**
   - Fragile X syndrome.

POST KALA-AZAR DERMAL LEISHMANIASIS (PKDL)

CHIEF COMPLAINTS

- Several hypopigmented lesions all over the body for … years
- Few nodules on the face and ulcer on the lower part of the right leg for … years
- Reddish skin lesions over face and upper arms for … months.

HISTORY

History of present illness: The patient states that he noticed several round hypopigmented skin lesions all over the body for the last … years. Initially, there were few non-itchy and painless lesions on the trunk. These slowly spread all over the body. He also noticed few painless nodular lesions of variable size and shape over the face, ear lobule and chin, some of which are gradually increasing in size. He also complains of two leg ulcers on the medial aspect of lower part of right leg that started as a small papule, became nodular and then ulcerated. These are slightly painful, itchy, and did not heal with local and systemic antibiotic therapy. For the last … months, the patient has also noticed few reddish skin lesions over the face and upper arms. There is no history of loss of appetite or weight loss. His bladder and bowel habits are normal.

History of past illness: He suffered from kala-azar (leishmaniasis) … years back and was treated with 20 injections of sodium stibogluconate.

Family history: Mention according to the patient's statement.

Personal history: He is a nonsmoker, nonalcoholic. There is no history of exposure.

Socioeconomic condition: Mention according to the patient's statement.

Treatment history: For the present problem, he has taken many antibiotics as prescribed by various doctors, but his condition did not improve.

GENERAL EXAMINATION

- The patient is anxious
- Mildly anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia, edema
- There is no thyromegaly or lymphadenopathy
- Pulse: 80/min
- Blood pressure: 120/80 mm of Hg
- Temperature: 98ºF
- Respiratory rate: 20/min.

Integumentary System

1. **Skin:**
   - Inspection:
     - There are multiple nodules of various size and shape on the nose, cheeks and ear lobules. These are pale, pink and wart-like.
     - Reddish lesions of various sizes and shapes are present on the face and flexor aspect of both forearms.

- There are bilateral, symmetrical, multiple hypopigmented macules and patches of various shape and size, seen on both the extremities and trunk. There is no scaling.
- There are two ulcers measuring 3 cm × 2.5 cm and 1.25 cm × 1.5 cm, situated on the anterolateral aspect of right leg near ankle. These are round in shape with irregular margin. Base is covered with crust. There is some oozing. Surrounding skin is hyperpigmented and erythematous.

♦ Palpation: Nodules are firm in consistency, nontender, mobile. Hypopigmented and erythematous macules and patches are also nontender with intact sensation. Edges of the ulcers are firm and slightly tender.

♦ Peripheral nerves are neither enlarged, nor tender. Peripheral pulses are normal.

2. **Mucous membrane:** Conjunctiva, oral mucosa and genital mucosa are normal.
3. **Hair:** Normal.
4. **Nails:** Discoloration of all fingernails.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, a 65 year old farmer, nonsmoker, nondiabetic, hailing from …, presented with several hypopigmented, non-itchy, painless skin macules and patches on the trunk for the last … years that slowly spread all over the body. He also noticed few painless nodular lesions of variable size and shape over the face, ear lobule and chin, some of that are gradually increasing in size. The patient also complains of two leg ulcers on the medial aspect of lower part of right leg that started as a small papule, became nodular and then ulcerated. These are slightly painful, itchy, and did not heal with local and systemic antibiotic therapy. For the last … months, the patient also noticed few reddish skin macules and patches over the face and upper arms.

The patient had suffered from kala-azar about … years back and was treated with 20 injections of sodium stibogluconate. For the current problem, he was treated with many antibiotics and local ointments from various local doctors, but his condition did not improve. There is no family history of similar illness.

On general examination – mention as above.

Examination of the integumentary system – as above.

Examination of other systems reveals no abnormalities.

My diagnosis is post kala-azar dermal leishmaniasis.

Q. How to **confirm** PKDL?

A. To confirm PKDL the following investigations may be done:

❖ Demonstration of amastigote form of LD bodies in smear prepared from biopsy material from nodular lesions (No LD bodies are found in depigmented lesion).

❖ PCR and monoclonal antibodies may detect parasites in more than 80% of cases.

Note Remember the following:

Serological tests and the leishmanin skin test are of limited value.

Q. What are your **differential diagnoses**?

A. As follows:

❖ Lepromatous leprosy

- Pityriasis versicolor
- Dermatomyositis
- SLE
- MCTD
- Others (rare)—Acne rosacea, syphilis (secondary), rhinophyma (irregular thickening of skin of nose with enlarged follicular orifice).

Q. What are the **points in favor** and **against** your differential diagnoses?

A. As follows:

Differential diagnoses	Points in favor	Points against
1. Lepromatous leprosy	» Bilateral, symmetrical hypopigmented macules and erythematous patches » Nodules over face and ear lobules	» Past history of kala-azar » Absence of madarosis » No nerve enlargement » Skin sensation—intact
2. Pityriasis versicolor	» Hypopigmented macules	» Long history, also history of kala-azar » Absence of pruritus, scaling » Presence of erythematous plaques
3. Dermatomyositis	» Only multiple skin lesions	» No muscular complaints, polyarthritis, proximal myopathy, heliotrope rash » No history of malignancy
4. SLE	» Only skin lesion	» History of kala-azar » No other systemic features or vital organ involvement » Does not fulfill the diagnostic criteria of SLE

RELATED QUESTIONS AND ANSWERS

Q. What is **post kala-azar dermal leishmaniasis**?

A. It is a non-ulcerative cutaneous lesion that occurs after treatment and apparent recovery from visceral disease. Initially, the lesions start as macules, become erythematous, followed by wart-like nodular lesions. It mainly involves the face, especially around the chin, also ear lobules. There may be butterfly like distribution of the lesion. Hypopigmented macules can occur in all parts of the body. No systemic symptoms and no spontaneous healing. Amastigotes are scanty in the lesion.

Note Remember the following:

In a small proportion of patients with PKDL, there is no preceding history of visceral disease suggesting a subclinical infection.

Q. How many **forms** are found in PKDL?

A. It is found in two forms:

1. African form (Sudanese form):
   - About 50% patients with visceral leishmaniasis develop PKDL. In Sudan, children are more affected than Indian subcontinent.
   - This may develop concurrently with visceral leishmaniasis or within 6 months afterwards.
   - The lesions are composed of discrete papules on the cheeks, chin, ears, extensor surfaces of forearms, buttocks and lower legs.
   - In addition to dermatological features described above, measles like maculopapular rash may develop all over the body.
   - It improves spontaneously in 3/4th cases within 1 year.
   - Leishmanin test is positive.
   - Histology reveals tuberculoid type with scanty parasites.
2. Indian form:
   - In Indian type, PKDL occurs in a small minority of patients 6 months to > 3 years after initial infection.
   - Lesions appear on the face, trunk, extremities (confused with lepromatous leprosy).
   - These are progressive and seldom heal spontaneously.
   - Tongue, palate and genitalia may be involved.
   - There may be lymphadenopathy but viscera are spared and there is no evidence of relapse of previous systemic infection.
   - Leishmanin test is negative.
   - Histopathology reveals differentiated infiltrate of chronic inflammatory cells with variable number of parasites in dermal macrophage.

Q. What are the **mechanisms** of PKDL?

A. After treatment, visceral infection disappears, but there is persistence of skin infection. After variable period, skin resistance is lost with resurgence of old infection that causes PKDL. It is considered as an important parasitic reservoir and source of transmission of kala-azar.

Q. How to **treat** PKDL?

A. As follows:

- Injection sodium stibogluconate (given in cycle), 20 mg/kg daily for 20 days. After 10 days interval, the injection is repeated. Totally 6 cycles are needed with an interval of 10 days.
- If a second course is required, it should be given after an interval of 2 months.
- In Sudan, sodium stibogluconate is given for 2 months.
- Several courses of amphotericin B infusion may also be given.
- Miltefosine may also be effective in PKDL.

Note Remember the following:

Treatment is always needed in Indian PKDL. In Sudan, most cases cure spontaneously, but severe and chronic cases should be treated.

Q. What are **other drugs** that can be given in PKDL?

A. Systemic drugs that are reported to be effective are ketoconazole, itraconazole, rifampicin and dapsone.

Note Remember the following:

Pentamidine is ineffective in PKDL.

Q. What are the **types** of lesions in PKDL?

A. These are mainly of 3 types:

1. **Macular:** May be hypopigmented, depigmented, hyperpigmented or erythematous (butterfly like rash, which is aggravated by sunlight).
2. **Elevated lesion:** Papular, nodular, plaque, hypertrophic, verrucous (around nose), xanthomatous around chin, fibroid around calf muscle.
3. **Ulcerative:** Rarely in nodular lesions.

Q. What are the **differential diagnoses** of PKDL?

A. The differential diagnoses vary according to the type of lesion:

1. **Macular:**
   - Lepromatous leprosy
   - Pityriasis versicolor
   - Pityriasis alba
   - Vitiligo
   - Nutritional dyschromia.
2. **Plaque:**
   - Lepromatous leprosy
   - Sarcoidosis
   - Deep mycosis
   - Tertiary syphilis
   - Leukemia cutis
   - Mycosis fungoides.
3. **Nodular:**
   - Lepromatous leprosy
   - Neurofibromatosis
   - Eruptive xanthoma
   - Familial lipomatosis
   - Sarcoidosis
   - Deep mycosis
   - Tertiary syphilis
   - Leukemia cutis
   - Mycosis fungoides.

Q. What are the **complications** of PKDL? **Why treatment** is given?

A. The PKDL itself has no complication other than disfigurement. PKDL patients serve as an important source of infection. Treatment should be given for the benefit of the community.

Q. What are the **differences** between PKDL and lepromatous leprosy?

A. As follows:

Points	PKDL	Lepromatous leprosy
1. Induration	Usually absent	Usually present
2. Loss of eyebrows	Absent	Present
3. Nerve enlargement	Absent	Present
4. Sensation	Intact	Impaired
5. Lymphadenopathy	May be present	Absent

Contd...

Contd...

6. Visceral involvement	Spared	Involved
7. Slit skin smear	LD bodies	AFB
8. Complication	No complication except reservoir	Many complications, such as nerve damage, claw hand, foot drop, iritis, iridocyclitis, involvement of liver, spleen, testicles, etc.

Q. Which form of PKDL contains **amastigote** form of parasite?

A. Amastigotes can be found in warty papular eruptions.

Q. Which type of patients usually develops **Indian form** of PKDL?

A. There is evidence that patients who will develop this condition have marker interleukin-10 in their keratinocytes and sweat glands.

LEPROMATOUS LEPROSY

CHIEF COMPLAINTS

- Multiple nodular lesions on ear lobe, face, forearm and legs for … months
- Hypopigmented lesions on both side of nose for … months
- Generalized weakness for … months.

HISTORY

History of present illness: The patient states that he was alright … months back. Since then, he noticed some nodules on different parts of the body, first on the front of the legs and dorsum of feet and later on the face, ears and forearms. These nodules are painless, non-itchy and without any discomfort. There are also few painless, non-itchy hypopigmented lesions on both sides of nose for … months. He does not feel any abnormal sensation over these lesions.

The patient also complains of generalized weakness for … months for which he is unable to perform his daily duties. There is no history of fever, arthralgia, mouth ulcer, etc. His bowel and bladder habits are normal.

History of past illness

Family history

Personal history

Socioeconomic condition

Drug history: Mention according to the statement of the patient.

GENERAL EXAMINATION

- Appearance normal
- Mildly anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia, edema
- No thyromegaly or lymphadenopathy
- Pulse: 88/min
- Blood pressure: 110/70 mm of Hg
- Temperature: 98ºF
- Respiratory rate: 18/min.

Integumentary System

1. **Skin:**
   - Inspection:
     - Multiple nodules of variable size and shape are present on ears, face, forearms, legs and feet that are bilateral and symmetrical.
     - There are also hypopigmented macules on both sides of nose that are ill defined and blend into the surrounding skin.
   - Palpation:
     - The nodules are nontender, firm in consistency and without any loss of sensation.
     - The hypopigmented macules are nontender. There is no loss of sensation.

2. **Hair:** Hair is lost on the outer-third of the eyebrows.
3. **Mucous membrane:**
   - Conjunctiva—normal
   - Oral mucosa—normal
   - Mucosa—normal.

Nervous System

- Supraorbital, great auricular, median, ulnar, radial, lateral popliteal and posterior tibial nerves are thickened bilaterally, but nontender
- There is no loss of sensation
- Reflexes are normal.

Examination of other systems reveals no abnormalities.

SALIENT FEATURE

Mr …, 50 years old, shopkeeper, normotensive, nondiabetic, hailing from …, was admitted into the hospital with the complaints of multiple nodular lesions on ear lobe, face, forearm and legs for … months and hypopigmented lesions on both side of nose for … months. The nodules first started on the front of the legs and dorsum of feet. Later, these lesions involved the face, ears and forearms. These are not associated with pain, itching or any discomfort. There are also few painless, non-itchy hypopigmented lesions on both side of nose for … months. He does not feel any abnormal sensation over these lesions. The patient also complains of generalized weakness for … months for which he is unable to perform his daily duties. There is no history of fever, arthralgia, mouth ulcer, etc. His bowel and bladder habits are normal. The patient was treated with vitamins and different types of creams and ointments by local physicians. There is no family history of similar illness.

On general examination – (mention as above).

On examination of the integumentary system – (mention as above).

Examination of other systems reveals no abnormalities.

My diagnosis is lepromatous leprosy.

Q. Why your diagnosis is lepromatous leprosy?

A. Because:

- The patient is from endemic zone
- Typical nodular lesion (leonine facies), hypopigmented macules and thickening of multiple nerves are highly suggestive.

Q. What are your **differential diagnoses**?

A. As follows:

- PKDL
- Neurofibromatosis
- Others: Sarcoidosis, drug rash, acne rosacea, dermatomyositis, SLE.

Q. What are the **points in favor** and **against** your differential diagnoses?

A. As follows:

Differentials	Points in favor	Points against
1. PKDL	Bilaterally symmetrical nodules and macules on face, ears, forearms and legs	No history of kala-azar in the past All peripheral nerves are thickened
2. Neuro-fibromatosis	Multiple nodules all over the body	No family history Nodules are firm in consistency Buttonholing sign absent Café au lait macule absent

Q. What specific **investigations** are done to diagnose (confirmatory) leprosy?

A. As follows:

- Demonstration of acid fast bacilli from slit skin smear, nasal scraping or biopsy material from skin or thickened nerve (Slit skin smear is prepared by Ziehl-Neelson method using 5% sulfuric acid. In developed countries, Fite-faraco stain is used).
- Skin biopsy for histopathology.

Q. What are the **histological findings** in leprosy?

A. As follows:

- In tuberculoid type, epithelioid granuloma may be found.
- In lepromatous leprosy, *M. leprae* may be found in skin macrophage (also Schwann cells and perineurium).

Q. What are the other **investigations** done to diagnose leprosy?

A. As follows:

- Histamine test: A drop of 1:1000 solution of histamine is put into the test area and outside area. A pin prick is made with each drop. A wheal forms, but red flare is absent in the affected area.
- Methacholine test: Skin is painted with 2% iodine. 1 mL of methacholine is injected intradermally in the affected area. Powder starch is dusted over the part. Powder turns blue by the interaction of sweat and iodine in the unaffected area that is absent in the affected area.
- Lepromin test to assess immune status.
- Newer diagnostic test:
  - Fluorescent lepromin antibody absorption test—low specificity.
  - Antibody against PGL-1, lipoarabinomannan and the protein antigens of *M. leprae*. PGL-1 antibody is positive in 90% of multibacillary, 40 to 50% of paucibacillary and 5 to 10% of healthy controls.
  - PCR.

Q. What are the **supportive investigations** of leprosy?

A. As follows:

- Full blood count (may be anemia, lymphopenia, high ESR because of hyperglobulinemia).
- Urine RME (may be proteinuria due to focal glomerulonephritis).
- Increased serum lysozyme and angiotensin converting enzyme due to accumulation of macrophages that synthesize these proteases.
- Increased FSH and LH and decreased testosterone (due to involvement of testicles).
- Organ specific antibodies against thyroid, nerve, testis and gastric mucosa.
- Nonorgan specific—RA, ANA, biological false positive test for syphilis.

Q. How can you **diagnose** leprosy?

A. As follows:

- Clinically leprosy can be diagnosed on the basis of two out of 3 findings:
  - Anesthesia of a skin lesion or in the distribution of a peripheral nerve or over dorsal surfaces of hand and feet.
  - Thickened nerve at the site of predilection.
  - Typical skin lesion.
- By demonstration of AFB in slit skin lesions.
- Histology: Typical of leprosy.

RELATED QUESTIONS AND ANSWERS

Q. What is **leprosy?**

A. Leprosy is a chronic granulomatous disabling disease caused by *Mycobacterium leprae* affecting the peripheral nerves, skin, mucous membrane, anterior segment of eye, bone and viscera. It is mildly communicable with good prognosis, if treated early and adequately.

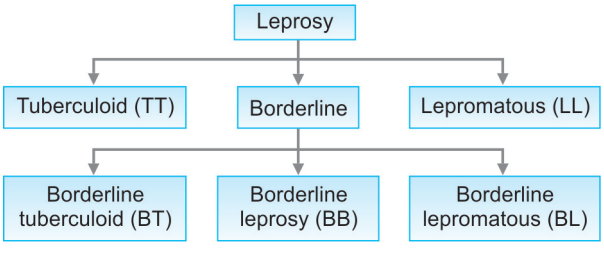
M. leprae is a Gram-positive, acid fast and alcohol fast bacillus, also called Hansen's bacillus. Man is the only reservoir of infection. Route of transmission—nasal, oral, sometimes skin contact (if ulcerated).

Q. What are the types (or **classification)** of leprosy?

A. There are five types (according to Ridley and Jopling):

- Tuberculoid leprosy (TT)
- Borderline tuberculoid (BT)
- Borderline-borderline leprosy (BB)
- Borderline lepromatous leprosy (BL)
- Lepromatous leprosy (LL).

Depending on the cell mediated immunity (CMI), leprosy is divided into 2 polar forms and a borderline form.



Also, classified into **two types:**

- Paucibacillary: Few organisms in tissue. Skin smear for *M. leprae* bacilli is negative or few (found in TT and BT).
- Multibacillary: Large number of organisms in tissue. Skin smear for *M. leprae* bacilli is positive (found in BT, all BB, BL and LL).

Q. What are the **findings** in different types of leprosy?

A. As follows:

Points	Tuberculoid (TT)	Borderline tuberculoid (BT)	Borderline (BB)	Borderline lepromatous (BL)	Lepromatous leprosy (LL)
1. Host resistance	High resistance	Unstable resistance			No resistance
2. Lesions	One to three	Few	Few or many Asymmetrical	Many	Numerous and symmetrical
3. Smear for bacilli	0	1+	2+	3+	4+
4. Lepromin test	3+	2+	+	±	0
5. Histology	Epitheloid cells, nerve destruction, sarcoid like granuloma	Decreasing	Decreasing	Increasing foam cells, xanthoma	Histocytes granuloma

Q. What are the **differences** between tuberculoid and lepromatous leprosy?

A. As follows:

Points	Tuberculoid	Lepromatous
1. Number	1 to 5	Numerous
2. Distribution	Asymmetric, anywhere especially face, limb and trunk (sparing scalp, axilla, perineum)	Symmetrical except spared areas
3. Margin	Well-defined	Ill-defined
4. Lesion	Plaque or macule	Macule, plaque, nodule and infiltration
5. Size	Usually large	Usually small
6. Anesthesia, autonomic loss and nerve enlargement	Early and marked, localized to the lesional skin or major peripheral nerve	Late and extensive
7. Skin texture	Dry, hard, pebbled	Smooth, shiny, normal texture
8. Hair growth	Absent in lesion	Normal
9. Mucosal involvement	Absent	Common
10. Bacillary index	Absent	Present in large number
11. Lepromin test	Strongly positive	Negative
12. Other organ involvement	Nil	Eye, bone, testis, kidney, reticuloendothelial system is involved

Q. What are the **differential diagnoses** of leprosy?

A. As follows:

1. Macular lesion:
- Vitiligo
- Pityriasis versicolor
- Pityriasis alba
- PKDL
- Healed herpes zoster
- Nevus anemicus
- Nutritional dyschromia.

2. Plaque type lesion:
- Lupus vulgaris
- Lupus erythematosus
- Tinea circinata
- Psoriasis
- Seborrheic dermatitis
- Annular syphilides
- Sarcoidosis
- PKDL.

3. Nodular:
- PKDL
- Neurofibromatosis
- Cutaneous leishmaniasis
- Mycosis fungoides
- Leukemia cutis
- Sarcoidosis
- Tertiary syphilis.

Q. What are the causes of **sensory impairment** with or without muscle atrophy?

A. As follows:
- Peripheral neuropathy due to any cause
- Cord compression due to any cause (loss of sensation below the level of lesion)
- Primary amyloidosis of peripheral nerve
- Congenital sensory neuropathy
- Peroneal muscular atrophy
- Trauma
- Cervical rib
- Syringomyelia
- Herpes zoster
- Thalamic lesion
- Functional.

Q. What are the **differences** between leprosy and syringomyelia?

A. As follows:

Points	Syringomyelia	Leprosy
1. Cause	Elongation of central canal with compression of lateral tract	Infectious disease caused by *M. leprae*

Contd...

Contd...

2. Site	Mainly upper limb, thumb, index and middle finger	Anywhere but sparing the axilla, perineum and scalp
3. Pattern of anesthesia	Dissociate anesthesia (loss of pain and temperature and intact tactile sensation)	Sequential loss of temperature, light touch, pain and deep touch sensations
4. Histamine and methacholine test	Positive	Negative

Q. What are the causes of **claw hand**?

A. As follows:
- Motor neuron disease
- Syringomyelia
- Charcot Marie Tooth disease
- Poliomyelitis
- Rheumatoid arthritis (in advanced stage)
- Trauma
- Dupuytren's contracture
- Congenital flexion of fingers.

Q. What are the causes of **neuropathic ulcer**?

A. As follows:
- Diabetes mellitus
- Leprosy
- Peripheral neuropathy due to any cause
- Syringomyelia
- Amyloidosis
- Porphyria
- Tabes dorsalis
- Planter corn.

Q. What are the causes of **nerve enlargement**?

A. Causes are:
- Leprosy
- Hereditary hypertrophic neuropathy
- Amyloidosis
- Acromegaly
- Sarcoidosis
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Repeated friction or trauma
- Neurofibromatosis.

Q. What is **leonine face**? What are the **causes** of it?

A. Leonine face is characterized by facial skin thickening associated with papules, nodules or diffuse infiltration in the skin that is called leonine face. It resembles the face of a lion. There may be depressed bridge of the nose, broad nose with nasal collapse (saddle nose). Lateral 1/3rd of eyebrows may be lost (called madarosis). Causes are:
- Lepromatous leprosy
- PKDL

- Mycosis fungoides
- Sezary syndrome
- Leukemia cutis
- Mucinosis
- Paget's disease of bone
- Mastocytosis
- Lichen myxedematosus.

Q. What are the causes of **saddle nose?**

A. As follows:

- Lepromatous leprosy
- Wegener's granulomatosis
- Lupus vulgaris
- Congenital syphilis
- Idiopathic midline granuloma.

Q. Which **nerves** are commonly involved in leprosy? Where are they **palpated?**

A. As follows:

- Facial nerve: Crossing the zygomatic arch
- Great auricular nerve: Posterior triangle of the neck
- Radial nerve: In the radial groove of humerus at the insertion of deltoid muscle
- Radial cutaneous nerve: In the wrist
- Ulnar nerve: In elbow, in between the medial epicondyle and olecranon process
- Median nerve: Middle of the front of wrist
- Lateral popliteal or common peroneal nerve: Around the neck of fibula
- Posterior tibial nerve: Ankle, a little below and posterior to medial malleoli.

Q. What is **madarosis**? What are the **causes**?

A. It is the loss of hair from the outer third of eyebrow. Causes are:

- May be a normal finding (common cause)
- Lepromatous leprosy
- Hypothyroidism
- Secondary syphilis
- Local fungal infection
- Follicular mucinosis
- As a part of alopecia.

Q. What are the causes of **anesthesia in skin**?

A. As follows:

- Leprosy
- Syringomyelia
- Trauma
- Tabes dorsalis
- Follicular mucinosis
- Diabetes mellitus
- Congenital sensory neuropathy.

Q. What are the lesions that show **central clearing**?

A. As follows:

- Tinea circinata

- Tuberculoid leprosy
- Granuloma annulare
- Parakeratosis
- Secondary syphilis
- Psoriasis
- Lichen planus
- Lupus vulgaris
- Sarcoidosis.

Q. How to **treat** leprosy?

A. WHO recommended protocol is as follows:

- **Paucibacillary** (three to five skin lesions, skin smear negative or few, tuberculoid and BT)—Rifampicin 600 mg monthly (supervised) **plus** dapsone 100 mg daily (self-administered) for 6 months.
- **Paucibacillary single lesion—**Rifampicin 600 mg **plus** ofloxacin 400 mg **plus** minocycline 100 mg, in single dose (ROM therapy).
- **Multibacillary** (more than five skin lesions, skin smear positive, BT, all BB, BL and LL)—Rifampicin 600 mg and clofazimine 300 mg monthly (supervised) **plus** dapsone 100 mg and clofazimine 50 mg daily (self-administered) for 12 months or until the findings on smear are negative (may be up to 24 months), whichever is longer.

Common **side effects** of anti-leprosy drugs are:

- Dapsone: Hemolytic anemia, agranulocytosis, exfoliative dermatitis, hepatitis, hypoproteinemia, psychosis.
- Clofazimine: Red coloration of skin, urine and body secretions, pruritus, anorexia, nausea, vomiting, abdominal pain.

Q. What are the **antigens** of leprosy?

A. As follows:

- **Phenolic glycolipid (PGL-1):** Present in the waxy exterior of bacteria and is a target of antibody response.
- **Lipoarabinomannan:** A lipoglycan is inserted into the cell membrane of *M. leprae* and courses the outer membrane. It is a target of both antibody and T-cell response.
- Highly immunologic proteins are located in the cytoplasm and are associated with the cell wall. These include highly conserved immunologic proteins of molecular mass 10 KD, 65 KD, and 70 KD each bearing *M. leprae* specific and mycobacterial cross reactive epitope.

Q. What are the **atypical presentations** of leprosy?

A. As follows:

1. In tuberculoid leprosy:
   - Pure neural leprosy
   - Tenosynovitis—painful swelling over the hands of one or both hands, rarely dorsum of foot. It may be a complication of type I reaction, but commonly associated with other evidence of BT
   - Spontaneous ulceration of skin because of exaggerated hypersensitivity of type I reaction.
2. In lepromatous leprosy:
   - Single nodule
   - Histoid leprosy—so called because microscopic appearance shows spindle shaped cells resembling dermatofibroma. They are well-defined hemisphere up to 3 cm in diameter.

They do not extend deeply into the skin, but feel like a button in the superficial dermis. Well-defined edge, shiny coppery red in color
- Spontaneous ulceration
- Lucio leprosy.

Q. What are the **complications** of leprosy?

A. Complications can be divided into:

I. Complications due to massive invasion of tissues by *Mycobacterium leprae*:
1. Ocular:
   - Miliary lepromat
   - Nodular lepromat
   - Chronic granulomatous iritis
   - Acute diffuse iridocyclitis
   - Corneal opacity
   - Avascular keratitis
   - Interstitial keratitis
   - Pannus formation.
2. Mucous membrane involvement:
   - Nose—chronic nasal congestion, perforation of nasal septum with collapse of nasal bridge, saddle nose deformity
   - Nodules in vocal cords, produces hoarseness of voice
   - Loss of upper incisor teeth deformity.
3. Visceral involvement: Mainly involves lymph nodes, bone marrow, liver, spleen. Testicular atrophy with resultant gynecomastia and premature osteoporosis.

II. Complications due to nerve damage:
- Sensory—anesthesia
- Motor—wasting of muscles, paralysis, claw hand, wrist drop, foot drop, lagophthalmos, mask face
- Autonomic—dry skin, crack, fissure, ulcer
- Secondary complication following nerve damage includes tissue necrosis, plantar ulceration, secondary bacterial cellulitis, osteomyelitis, progressive loss of digits of hands and feet, malum perforans pedis.

III. Complications due to reaction:
1. Type I –
   - Rapid swelling of one or more nerves with pain and tenderness at the site of nerve swelling and nerve abscess
   - Edema of hands, feet and face
   - Claw hand, foot drop, facial palsy.
2. Type II –
   - Iritis, iridocyclitis, keratitis, conjunctivitis
   - Epistaxis, muscle pain, bone pain, joint pain, lymphadenitis, epididymo-orchitis
   - Hepatomegaly, pleuritis, nephritis, orchitis
   - Paralysis occurs but does not threaten so quickly.

IV. Complication due to drug resistance: Most dapsone resistance is secondary and occurring up to 15% of cases of multibacillary patients. It may start as typical lepromatous like or new discrete lesions appear against a background of healed lesions.

Q. What is **lepra reaction**?

A. Lepra reactions are immunologically mediated acute reactions that occur in patients with the borderline or lepromatous leprosy, usually during treatment. It may be the first manifestation of the disease.

It may be insidious or rapid, destroying the affected tissue within hours. It is of two types: type I and type II.

Type I lepra reaction (reversal): It is a delayed hypersensitivity reaction (type IV) that occurs in 30% borderline patients (BT, BB and BL). It occurs spontaneously or may be precipitated by treatment. There is rapid swelling of one or more nerves with pain and tenderness at the site of nerve swelling. Nerve function is lost rapidly, foot drop may occur overnight. Also, there may be claw hand, facial palsy, etc. Skin lesions become erythematous and swollen and new skin lesion may appear. There may be edema of hands, feet and face. Reversal of reactions may occur spontaneously, after starting treatment and after completion of multidrug therapy.

Treatment:

- In mild case, aspirin 600 mg 6 hourly.
- In severe case, prednisolone 40 to 60 mg daily. The dose should be reduced by 5 mg/day each month, should be tapered over 3 to 6 months.
- Clofazimine can be added upto 300 mg daily. If fails, cyclosporine 5 to 10 mg/kg may be given.
- Treatment of leprosy should be continued.

Type II lepra reaction (erythema nodosum leprosum, ENL): Type II lepra reaction, which is due to immune complex deposition (type III hypersensitivity reaction). It occurs in BL and in LL patient who produce antibodies and have a high antigen load. It is characterized by fever, arthralgia and crops of small pink painful nodules on the face and limbs. Iritis, iridocyclitis, keratitis, conjunctivitis and episcleritis are common. Other signs are neuritis, orchitis, myositis, nephritis, epistaxis, pleurisy, bone pain, arthritis, lymphadenitis and hepatomegaly. ENL may be the first manifestation of leprosy in 50% lepromatous and 25% borderline lepromatous leprosy, either during the course of the disease or more commonly in the second year of treatment. ENL may continue intermittently for several years.

Treatment:

- In mild cases, analgesic (aspirin 600 mg 6 hourly).
- In severe cases, thalidomide (100 mg 6 hourly). When symptoms improve, reduce the dose slowly over weeks or months, maintenance dose is 50 to 100 mg daily. It is a potent teratogenic drug (contraindicated in pregnancy).
- If thalidomide is not available, prednisolone (40 to 60 mg) should be given, and reduce the dose over 1 to 6 months. Chloroquine can also be used.
- The dose of clofazimine (300 mg daily) should be increased for few weeks. It will reduce the reaction and help to reduce the dose of prednisolone.
- Anti-leprosy therapy must be continued.

Q. How would you **differentiate** between two types of lepra reactions?

A. As follows:

Points	Type I reversal or downgrading	Type II
1. Type	» Mostly in BT, BB, BL	» Mostly in LL
2. Onset	» Upgrading—during first 6 months of therapy in BT and BB but longer duration in BL » Downgrading—in untreated or in interrupted treatment	» After 1 or 2 years of therapy or untreated case of long duration

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3. Cause	» Upgrading or reversal—increase in CMI » Downgrading—decrease in CMI (type 1V)	» Immune complex syndrome due to precipitation of antigen antibody complex in tissue spaces, blood and lymphatic vessels (type III)
4. Clinical features	» Some or all of the existing lesions show signs of inflammation	» Existing lesions do not show clinical aggravation » Sudden appearance of crops of evanescent tender nodules or plaques » May become vesicular, pustular, bullous or gangrenous
5. Associated features	» Rapid swelling of one or more nerves. Nerve abscess may occur	» Nerve damage does not threaten so quickly » Commonly associated features are iritis, iridocyclitis, epistaxis, muscle pain, bone pain, nerve pain, joint pain, lymphadenitis, epididymo-orchitis, proteinuria
6. Histology	» Upgrading—increase in lymphocytes, epithelioid cells and giant cells. The number of bacilli decreases » Downgrading—macrophages and increase no of bacilli	» Large number of polymorphs » Bacilli numerous, fragmented and granular
7. Lepromin test	» Upgrading—positive » Downgrading—negative	» Negative
8. Hematological finding	» Nil	» IgG, IgM, C2, C3
9. Course	» Seldom persists more than a few months	» Mild ENL disappears rapidly but severe ENL may persist for years and may result in death

Q. What is bacterial or **bacteriological index** (BI)?

A. It indicates the density of leprosy bacilli in smears and includes both living (solid staining) and dead (fragmented or granular) bacilli. Bacteriological index in LL is 5 to 6 and in TT is 0.

Q. What is **morphological index** (MI)?

A. It is the percentage of presumably living bacilli in relation to the total number of bacilli in the smear.

PITYRIASIS RUBRA PILARIS

CHIEF COMPLAINTS

- Widespread papular eruption for … years
- Scaling patches for … years
- Thickening of palms and soles for … years.

HISTORY

History of present illness: The patient states that he was alright … years back. Since then, he noticed multiple papules on different parts of the body that initially started on the dorsum of phalanges and later gradually spread to the neck, trunk and extensor surface of the extremities. He also noticed yellowish scaling patches on the scalp for … years. There are also widespread areas of sharply marginated patches of various sizes on both sides of the body. The lesions are slightly itchy. The patient also noticed gradual thickening of palms and soles that is painless and non-itchy. His nails are rough and thickened. The patient observed development of papules at the sites of scratches and also at the site of injury. There is no history of fever or joint pain or mouth ulcer. The lesions are not aggravated by sun exposure. His bowel and bladder habits are normal.

History of past illness

Treatment history

Family history

Personal history

Socioeconomic condition: Mention according to the statement of the patient.

GENERAL EXAMINATION

- Appearance normal
- Mildly anemic
- No jaundice, cyanosis, clubbing, edema, dehydration, koilonychia, leukonychia
- Lymph nodes and thyroid gland are not enlarged
- Pulse: 92/min
- BP: 90/60 mm Hg
- Temparature: 98ºF.
- Respiratory rate: 20/min.

Integumentary System

1. **Skin:**
   - Inspection:
     - Small, pinhead, reddish brown, follicular papules that are topped by central horny plug and disseminated yellowish scaling patches are present almost all over the body, especially on backs of the first and second phalanges, the sides of the neck, trunk and extensor surface of the extremities. Patches look like exaggerated goose flesh.
     - There are islands of normal skin within the affected areas.

- Koebner phenomenon is found on the back in a scratch mark.
- Scalp shows erythema and scaling.

♦ Palpation:
- Patches feel like nutmeg
- Palms and soles are uniformly thickened. Hyperkeratosis extends up to the sides forming sandal appearance.

2. **Nails** are rough, thickened, brittle, striated.
3. **Mucous membrane:** Not involved.

Examination of other systems reveals no abnormalities.

SALIENT FEATURE

Mr …, … years old, student, normotensive, nondiabetic, nonsmoker, hailing from …, presented with multiple papules on different parts of the body that initially started on the dorsum of phalanges and later gradually spread to the neck, trunk and extensor surface of the extremities. He also noticed yellowish scaling patches on the scalp for … years. There are also widespread areas of sharply marginated patches of various sizes on both sides of the body. The lesions are slightly itchy. The patient also noticed gradual thickening of palms and soles that is painless and non-itchy. His nails are rough and thickened. The patient observed development of papules at the sites of scratches and at the site of injury. There is no history of fever or joint pain or mouth ulcer. The lesions are not aggravated by sun exposure. His bowel and bladder habits are normal. He was treated with antihistamine tablets, vitamins and several ointments. There is no history of such illness in his family.

On general examination – (mention as above).

On examination of the integumentary system – (mention as above).

Examination of other systems reveals no abnormalities.

My diagnosis is pityriasis rubra pilaris.

Q. What are your **differential diagnoses?**

A. As follows:

❖ Psoriasis
❖ Lichen planus.

Q. What are the **points in favor** and **against** your differential diagnoses?

A. As follows:

Differential diagnoses	Points in favor	Points against
1. Psoriasis	» Papules and scaling patches » Koebner's phenomenon present	» Scales are not silvery white in color » Islands of normal skin within the affected areas » Plantar hyperkeratosis extends up to the sides
2. Lichen planus	» Papular eruption » Koebner's phenomenon present	» Absence of shiny, flat-topped violaceous papules » Oral mucosa is not involved

Q. What **investigations** do you suggest?

A. As follows:

1. Routine:
   - TC, DC, Hb%, ESR
   - Blood sugar
   - Urine R/M/E
   - Lipid profile (retinoids cannot be given in hyperlipidemia)
   - Liver function tests.
2. Skin biopsy for histopathology and DIF.

RELATED QUESTIONS AND ANSWERS

Q. What is **pityriasis rubra pilaris (PRP)**?

A. PRP is a chronic skin disease characterized by small follicular papules, disseminated, yellowish pink scaling patches and often solid palmoplantar hyperkeratosis.

Q. What are the **types** of PRP?

A. As follows:

- Type I – Adult onset classical
- Type II – Adult onset atypical
- Type III – Juvenile onset classical
- Type IV – Juvenile onset circumscribed
- Type V – Juvenile onset atypical
- Type VI – HIV associated.

Q. What is the **etiology** of PRP?

A. The exact etiology is unknown. The disease is usually transmitted as autosomal dominant trait in juvenile onset PRP. Histological and clinical features suggest that it is a vitamin deficiency disorder, particularly of vitamin A. Some patients have low serum levels of retinol binding protein. Both sexes are affected with equal frequency.

Q. What are the **histopathological and DIF findings** in PRP?

A. As follows:

- Skin biopsy for histopathology shows the following features (specimens should be obtained from skin sites where hair follicles are numerous):
  - Hyperkeratosis
  - Parakeratosis
  - Follicular plugging at the follicular orifice
  - Alternating vertical and horizontal parakeratosis in the interfollicular stratum corneum is said to be characteristic
  - Inflammatory infiltrate in the dermis is composed of mononuclear cells and mild.
- DIF is negative. It is done to differentiate from Lichen planus.

Q. What are the different **treatment** modalities in PRP?

A. As follows:

- Systemic retinoids are effective
- Isotretinoin in doses of 0.5 to 2 mg /kg /day for several months
- Vitamin A in doses of 300,000 to 500,000 units daily with vitamin E 400 units two or three times daily

- Systemic steroid can be given for acute short-term management
- Methotrexate 2.5 mg orally alternating one day with 5 mg the next
- Combination of isotretinoin or acitretin with low dose methotrexate
- Azathioprine is also effective
- In severe cases, extracorporeal photochemotherapy with systemic retinoids and cyclosporine.
- Treatment of secondary infection, if present.

Q. How would you **differentiate** between PRP and psoriasis?

A. As follows:

Points	PRP	Psoriasis
1. Age of onset	Bimodal, highest incidence is during first 5 years or between ages 51 and 55	2nd to 4th decade
2. Scales	Yellowish pink over the body Furfuraceus over scalp	Silvery white Adherent scale over scalp
3. Islands of normal skin	Present	Not common
4. Auspitz sign	Absent	Present
5. Keratoderma	Constant	Less common
6. Nail change	Striated, brittle, rough	Pitting, oil spots, subungual hyperkeratosis
7. Nail growth rate	Moderate increase	Marked increase
8. Histopathology – Munro's microabscess – Follicular plugging	 Absent Present	 Common Absent
9. Seronegative arthropathy	Very rare	Common
10. Response to UVB	Poor	Good
11. Response to corticosteroid	Poor	Positive
12. Response to methotrexate	Variable	Good

Q. What are the **differential diagnoses** of PRP?

A. Diseases that simulate PRP are:

- Psoriasis
- Lichen planus
- Phrynoderma
- Subacute cutaneous lupus erythematosus
- Dermatomyositis.

Q. What are the **complications** of PRP?

A. As follows:

- Exfoliative dermatitis
- Prolonged erythema
- Ectropion
- Peripheral edema

- High output cardiac failure
- Eruptive seborrheic keratosis.

Q. What are the diseases that **involve hair follicles**?

A. Follicular involvement can be classified into:

1. Infective folliculitis:
   - Bacterial—*Staphylococcus*, *Streptococcus*, *Pseudomonus*, *Proteus*, *Klebsiella*, follicular syphilides, follicular chancroid, lichen scrofulosorum (by *Mycobacterium tuberculosis*)
   - Viral—Herpes simplex
   - Parasitic—*Demodex folliculorum*
   - Fungal—Tinea capitis, Tinea barbae, pityrosporum folliculitis.
2. Noninfective:
   - Eosinophilic folliculitis
   - Perforating folliculitis
   - Pseudofolliculitis barbae
   - Keloidal folliculitis
   - Folliculitis decalvans
   - Acne vulgaris
   - Fox Fordyce's disease
   - Pityriasis rubra pilaris
   - Lichen plano pilaris
   - Phrynoderma
   - Kyrle's disease
   - Keratosis pilaris
   - Darier's disease
   - Lichen spinolosus.

Q. What are the diseases that show **disorders of keratinization**?

A. The following diseases show disorder of keratinization:

- Psoriasis
- PRP
- Exfoliative dermatitis
- Parapsoriasis
- Ichthyosiform disorder
- Darier's disease
- Parakeratosis
- Acrokeratosis verruciformis of Hopf.

Q. What are the causes of **palmoplantar keratoderma**?

A. Causes of palmoplantar keratoderma can be classified into the following:

1. Acquired type:
   - Psoriasis
   - PRP
   - Lichen planus
   - Contact dermatitis
   - Tinea pedis
   - Arsenical keratoses
   - Corn
   - Callus

- Wart
- Cancer associated paraneoplastic disorder
- Syphilis.

2. Hereditary:

- Hereditary palmoplantar keratoderma
- Punctate palmoplantar keratoderma
- Mal de Meleda
- Darier's disease
- Ichthyosis
- Pachyonychia congenita
- Dyskeratosis congenita.

Q. What are the types of **systemic retinoids**?

A. Widely used retinoids are:

First generation (nonaromatic):

- Isotretinoin
- Tretinoin.

Second generation (monoaromatic):

- Etretinate
- Acitretin.

Third generation (polyaromatic):

- Adapalene
- Tazarotene.

Q. What are the **indications** of systemic retinoids?

A. As follows:

- PRP
- Recalcitrant and nodulocystic acne
- Hidradenitis suppurativa
- Pustular and erythrodermic psoriasis
- Darier's disease
- Ichthyosis
- Gram-negative folliculitis
- Mycosis fungoidis
- Melanoma
- Multiple basal cell carcinoma.

Q. What **precautions** are to be taken before giving systemic retinoids?

A. As follows:

- Consent from the patient
- Contraception
- Documentation of absence of pregnancy
- Avoidance of smoking and alcohol
- Low fat diet to keep the lipid level normal.

Q. What are the **side effects** of retinoids?

A. Side effects of retinoids are:

1. **Cutaneous:**
   - Cheilitis
   - Conjunctivitis
   - Facial dermatitis
   - Dry eyes
   - Dry mouth
   - Xerosis with pruritus
   - Hair thinning and hair loss.
2. **Systemic:**
   - Teratogenicity
   - Pseudotumor cerebri (headache, papilledema)
   - Arthralgia
   - Osteoporosis
   - Premature epiphyseal closure and vertebral abnormalities.
3. **Laboratory:**
   - Hyperlipidemia.
   - Abnormal liver function test.

Q. What are the causes of **papulosquamous diseases**?

A. The following diseases are considered to be papulosquamous:

- Psoriasis
- PRP
- Parapsoriasis
- Pityriasis rosea
- Seborrheic dermatitis
- Lichen planus
- Secondary syphilides
- Subacute cutaneous lupus erythematosus
- Mycosis fungoides
- Sarcoidosis.

PEMPHIGUS VULGARIS

CHIEF COMPLAINTS

- Multiple blisters in different parts of the body for … months
- Painful ulcerations inside the mouth for … months
- Generalized weakness and loss of weight for … months.

HISTORY

History of present illness: The patient states that she was reasonably well … months back. Since then, she noticed multiple blisters in skin of different parts of the body. Initially blisters were few, starting over the groin, but gradually appeared in the scalp, face, neck, axilla and genitals. Some of the blisters ruptured spontaneously forming ulceration with oozing and bleeding. Later on, some lesions became covered with crusts. For the last … months, she also noticed few blisters inside the mouth that ruptured to form painful ulceration. The lesions increased in size, involved the lips and formed crusts. The patient also complains of generalized weakness, gradual weight loss, difficulty in swallowing and offensive odor in the mouth. There is no history of fever, joint pain, and bowel or bladder abnormality.

History of past illness

Treatment history

Family history

Personal

Socioeconomic condition

Drug history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient is ill looking and emaciated
- Moderately anemic
- No jaundice, cyanosis, clubbing, edema, dehydration, koilonychias, leukonychia
- Lymph nodes and thyroid gland are not enlarged
- Pulse: 108/min
- Blood pressure: 90/60 mm of Hg
- Temperature: 100 °F
- Respiratory rate: 24/min.

Integumentary System

1. **Skin:**
   - Multiple thin walled, flaccid bullae are present over scalp, face, neck, axilla, groin and genitals. Some are on normal skin and some are on erythematous bases.
   - Some of the bullae are ruptured forming denuded areas that enlarge by confluence.
   - In some bullae, there is clear fluid and in some, the fluid is hemorrhagic.
   - Denuded areas are partially covered with crusts.
   - Few areas of hyperpigmentation are present on the trunk that are indicative of healed lesions without scarring.
   - Nikolsky and Asboe-Hansen signs are positive (mention if any).

2. **Mucous membrane:**
   - Conjunctiva—normal
   - Oral cavity—multiple irregular ulcerations are seen in the oral mucous membrane and palate, few lesions on the lips and form heavy crusts. Partially detached membranous sheets cover the tongue
   - Vulva—multiple erosions within the mucosa of vulva.
3. **Nails:** Nails of index and little fingers of left side show paronychia around them.
4. **Hair:** Normal.

Note

Genital parts should be examined and mentioned, if there is any finding, e.g. erosions.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mrs …, 50 years, housewife, normotensive, nondiabetic, nonsmoker, hailing from …, presented with the complaints of multiple blisters in skin of different parts of the body for … months. Initially, the blisters were few, starting over the groin, but gradually appeared in the scalp, face, neck, axilla and genitals. Some of the blisters ruptured spontaneously forming ulceration with oozing and bleeding. Later on, some lesions became covered with crusts. For the last … months, she also noticed few blisters inside the mouth that ruptured to form painful ulceration. The lesions increased in size, involved the lips and formed crusts. The patient also complains of generalized weakness, gradual weight loss, difficulty in swallowing and offensive odor in the mouth. There is no history of fever, joint pain, and bowel or bladder abnormality. There is no history of taking any drugs responsible for this lesion.

On general examination – (mention as above).

On examination of the integumentary system – (mention as above).

Examination of other systems reveals no abnormalities.

My diagnosis is pemphigus vulgaris.

Q. What are your **differential diagnoses?**

A. As follows:

- Bullous pemphigoid
- Stevens-Johnson syndrome.

Q. What are the **points in favor** and **against** your differential diagnoses?

A. As follows:

Differential diagnoses	Points in favor	Points against
1. Bullous pemphigoid	» Blisters over the groin and axilla » Oral mucosa is involved	» Flaccid, thin walled, easily ruptured bullae » Denuded areas enlarging by confluence » More than one mucous membranes are involved » Nikolsky and Asboe-Hansen signs are positive

Contd...

Contd...

2. Stevens-Johnson syndrome	» Blisters on the trunk » Two mucous membranes are involved	» Absence of febrile prodrome, no history of drug, absence of target lesions

Q. What are the **investigations** done in pemphigus vulgaris?

A. As follows:

1. Routine:
   - FBC
   - Blood sugar
   - Urine RME
   - Liver function tests
   - Renal function tests.
2. Diagnostic:
   - **Skin biopsy** for histopathology and immunofluorescence test (early intact bullae < 12 hours duration should be taken with perilesional area).
   - Cytological (**Tzanck method)**—Smears are taken from the base of a bulla and (using Giemsa stain) is used for rapid demonstration of acantholytic cell (that shows no intercellular bridge, darkly staining cytoplasm and large nuclei surrounded by lightly staining halo).
   - **Direct immunofluorescence** shows intercellular deposition of IgG throughout epidermis (both involved and normal skin) or oral mucosa and C3 deposition in acantholytic area (net-like, honeycomb or mosaic pattern).

Histological findings:

- Acantholysis (separation of individual keratinocyte from one another)
- Superficial intraepidermal split
- Intraepidermal blister above basal layer (in pemphigus vulgaris) or subcorneal epidermal split (in pemphigus foliaceus)
- Acantholytic cells are found lining the bulla as well as lying free in the bulla cavity
- Eosinophilic spongiosis and occasionally neutrophilic spongiosis may be seen in the spongiotic epidermis in pemphigus vulgaris.

Q. How **biopsy and DIF materials** are collected?

A. A small early intact bulla should be taken. Site of biopsy is frozen with aerosol refrigerant spray so that the punch may include firm tissue. Tissue for biopsy is taken in test tube containing formalin. Normal appearing perilesional skin is taken for DIF in saline soaked gauze.

Q. How would you **treat** the patient?

A. As follows:

1. General measures:
   - Bed rest
   - Daily bath to remove thick crusts and foul odor
   - Maintenance of fluid and electrolyte balance and nutrition
   - Antibiotic and blood transfusion (if necessary).

2. Topical:
   - 1% silver sulfadiazine is applied topically
   - Antiseptic mouth wash and viscous xylocaine are to be applied in the mouth
   - Care of the eye.

3. Systemic:

- High dose prednisolone—100 to 200 mg/day. The dose should be tapered when remission occurs with no new blister. Maintenance dose is required for long time (may require lifelong treatment). If new blister occurs during treatment, the dose of prednisolone should be increased.
- **Other treatment:**
  a. IV methylprednisolone 1 g/day for 5 days (pulse therapy)
  b. Mycophenolate mofetil 1 to 1.5 g is given twice a day (commonly used as steroid sparing drug)
  c. Other drugs—azathioprine, cyclophosphamide, methotrexate, cyclosporine and dapsone
  d. In resistant case, IV immunoglobulin may be tried
  e. Biologic agents (infliximab, rituximab and etanercept)
  f. Extracorporeal photochemotherapy.

Prognosis: Prognosis is bad and recurrence is common with high mortality.

RELATED QUESTIONS AND ANSWERS

Q. What is **pemphigus vulgaris**?

A. It is an autoimmune blistering disease characterized by thin walled, flaccid, easily ruptured bullae that appear on both apparently normal skin and mucous membrane or on erythematous bases. On direct immunofluorescence test, it shows the presence of intercellular antibodies throughout the epidermis and oral epithelium.

Q. What are the **types** of pemphigus?

A. Pemphigus can be classified into:

1. Pemphigus vulgaris:
   - Pemphigus vegetans (localized)
   - Drug induced.
2. Pemphigus foliaceus:
   - Pemphigus erythematosus (localized)
   - Fogo selvagem (endemic)
   - Drug induced.
3. Paraneoplastic pemphigus.
4. IgA pemphigus.

Q. What are the **causes** of pemphigus vulgaris?

A. Exact etiology is unknown. Probable factors are:

- Autoimmunity, as suggested by the intercellular deposition of IgG and C3 complement in epidermis
- Genetic predisposition (associated with HLA DR4 and DR6)
- Drugs (penicillin, penicillamine, captopril, rifampicin, cephalosporin, pyrazolone, etc.)
- UV light, PUVA and ionizing radiation
- Increased incidence in myasthenia gravis and thymoma.

Q. What is the **pathogenesis** of pemphigus vulgaris?

A. Circulating antibody binds to cell surface glycoprotein that result in activation of plasmin, which causes enzymatic destruction of intercellular cement and desmosomes with formation of intraepidermal blister.

Q. What are the **presentations** of pemphigus vulgaris?

A. It is common in middle age, 50 to 60 years, and it is equally present in both sexes. The patient presents with:

- Thin-walled flaccid bullae that easily rupture, causing erosion, ulcer and crust formation with oozing and bleeding.
- Mouth ulcer is common (in 60%), also conjunctival and genital ulcer are noted.
- Ulcer heals slowly with hyperpigmented patch without scarring.

Q. What is **acantholysis**?

A. Acantholysis is loss of coherence between epidermal or epithelial cells.

1. Primary acantholysis occurs among unaltered cells as a result of dissolution of intercellular cement substance. It is seen in:
   - Pemphigus vulgaris
   - Pemphigus foliaceus
   - Benign familial pemphigus
   - Darier's disease.
2. Secondary acantholysis occurs among altered or damaged cells. It is seen in:
   - Viral vesicles
   - Impetigo
   - Subcorneal pustular dermatosis
   - Solar keratosis.

Q. What is the **bedside test** in pemphigus vulgaris?

A. As follows:

1. Nikolsky sign—Rubbing of unaffected skin results in separation of epidermis leaving a moist surface. This can be seen in:
   - Pemphigus vulgaris (common cause)
   - Staphylococcal scalded skin syndrome (SSSS)
   - Toxic epidermal necrolysis
   - Epidermolysis bullosa dystrophic
2. Bullae spread phenomenon or Asboe-Hansen sign. Pressure on the intact bullae gently forces the fluid to wander under the skin away from pressure site. It demonstrates the lack of cohesion.

Q. What are the **complications** of pemphigus vulgaris?

A. Secondary bacterial infection (pneumonia, septicemia), hypoproteinemia, side effects of systemic prednisolone.

Q. How do you **differentiate** between pemphigus vulgaris and pemphigus foliaceus?

A. As follows:

Points	Pemphigus vulgaris	Pemphigus foliaceus
1. Type of bullae	Flaccid or ruptured bulla on normal or erythematous skin	Flaccid bullae with exfoliation on erythematous skin only
2. Oral involvement	60% oral lesion	Oral lesion absent
3. Denuded area	Present	No denuded area, there will be crust, below that moist area is present that bleeds
4. General health	Affected	Not affected
5. Age	5th and 6th decade	4th and 5th decade
6. Histopathology	Suprabasal cleft and blister	Subcorneal cleft and blister
7. Antigen	Desmoglein 3 and 1	Desmoglein 1 and Plakoglobin

Q. What are the malignant diseases associated with **paraneoplastic pemphigus**?

A. As follows:

- Non-Hodgkin lymphoma
- Chronic lymphocytic leukemia
- Castleman's tumor
- Sarcoma
- Thymoma.

Q. What type of pemphigus is initiated by **infectious agents** carried by mosquito or black flies?

A. Brazilian pemphigus or Fogo Selvagem.

Q. What are the causes of **blisters** of the skin?

A. The causes of blisters are the following:

1. Infective:
   - Bacterial—bullous impetigo, SSSS, impetigo contagiosa, congenital syphilis
   - Viral—herpes simplex, herpes zoster, chicken pox
   - Fungal—bullous tinea pedis
   - Parasitic—bullous scabies.
2. Noninfective:
   - Autoimmune blistering—pemphigus vulgaris, bullous pemphigoid, dermatitis herpetiformis
   - Autoimmune connective tissue—bullous SLE
   - Metabolic—DM, primary systemic amyloidosis, porphyria cutanea tarda
   - Drugs—sulfonamide, tetracycline, penicillin, captopril, frusemide
   - Physical agents—burn, pressure, radiation, friction
   - Chemical agents—acid, alkali
   - Miscellaneous—bullous lichen planus, erythema multiforme, Stevens Johnson syndrome, lichen sclerosus atrophicus, irritant contact dermatitis.

Q. What are the causes of **hemorrhagic bullae**?

A. As follows:

- Pemphigus vulgaris
- Bullous pemphigoid
- Herpes zoster
- Toxic epidermal necrolysis
- Leukocytoclastic vasculitis
- Lichen sclerosus atrophicus
- Epidermolysis bullosa acquisita
- Primary systemic amyloidosis
- Epidermolysis bullosa simplex (ogna)
- Allergic granulomatosis
- Cutaneous manifestation of systemic candidiasis.

Q. What are the **autoimmune blistering diseases**?

A. As follows:

- Pemphigus with its variants
- Bullous pemphigoid
- Linear IgA dermatosis
- Dermatitis herpetiformis
- Herpes gestationis

- Cicatricial pemphigoid
- Epidermolysis bullosa acquisita
- Chronic bullous disease of childhood.

Q. What are the **causes** of bullous lesion in skin with mouth ulcer?

A. As follows:

- Pemphigus vulgaris
- Bullous pemphigoid
- Stevens Johnson syndrome
- Toxic epidermal necrolysis
- Behçet's syndrome
- Bullous SLE.

Q. What are the diseases that can be diagnosed by **DIF**?

A. DIF helps in the diagnosis of the following diseases:

- All autoimmune blistering diseases mentioned above
- SLE
- DLE
- Lichen planus
- Leukocytoclastic vasculitis.

Q. What are the **DIF findings in different diseases**?

A. As follows:

Diseases	Preferred biopsy site	Precipitated immunoreactants	Site	Pattern
1. Pemphigus vulgaris and foliaceus	Perilesional	IgG	Intraepidermal site (IES)	Net-like/ honeycomb/ lacelike/ mosaic
2. Pemphigus erythamatosus	Perilesional	IgG and C3	Intercellular and basement membrane zone (BMZ)	Net like or lace-like
3. IgA pemphigus	Perilesional	IgA	IES	Lace-like
4. Paraneoplastic	Perilesional	IgG and C3	IES and BMZ	Lace-like Linear or granular
5. Bullous pemphigoid	Perilesional	C3 (100%) and IgG (80%)	BMZ	Linear
6. Cicatricial pemphigoid	Perilesional	IgG and C3	BMZ	Linear
7. Dermatitis herpetiformis	Perilesional or normal	IgA with or without C3	BMZ at the tips of dermal papilla	Granular
8. Herpes gestationis	Perilesional	C3	BMZ	Linear

Contd...

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9. Epidermolysis bullosa acquisita	Perilesional	C3, IgG	BMZ	Linear
10. Bullous SLE	Perilesional	C3, IgG	BMZ	Linear
11. Lupus erythematosus	Lesional or normal	IgM, IgG, C3	BMZ	Granular
12. Linear IgA dermatosis	Perilesional	IgA	BMZ	Linear
13. Leukocytoclastic vasculitis	Lesional (early lesion)	IgM, IgG, C3	In vessel wall	Granular
14. Lichen planus	Lesional	IgM, less commonly IgA, IgG, C3	Subepidermally	Linear

BULLOUS PEMPHIGOID

CHIEF COMPLAINTS

- Multiple blisters over different parts of the body for … months
- Red patches over the trunk for … months
- Itching for … months.

HISTORY

History of present illness: The patient states that he was alright … months back. Since then, he has been suffering from multiple blisters over different parts of the body. The blisters at first appeared over forearms and gradually involved axilla, groin and front and back of trunk. Most of the blisters are large and tense, few are small. Some blisters have ruptured leaving denuded areas that have healed spontaneously. He also noticed erythematous patches over the front and back of the trunk, some of which healed spontaneously. There is no involvement of the mouth or genitalia.

The patient also complains of mild generalized itching for the same duration. He did not complain of difficulty in swallowing. There is no history of fever, joint pain, muscle pain or intake of any drugs prior to the appearance of these blisters. His bowel and bladder habits are normal.

History of past illness: He had similar attack 3 years back, but the lesions were sparse and recovered completely.

Family history

Personal history

Socioeconomic condition

Treatment history: Mention according to the statement of the patient.

GENERAL EXAMINATION

- The patient looks very ill and apathetic
- Mildly anemic
- No jaundice, cyanosis, edema, dehydration, clubbing, koilonychias, leukonychia
- No lymphadenopathy and no thyromegaly
- Pulse—98/min
- Blood pressure—110/70 mm of Hg
- Temperature—98 °F
- Respiratory rate—20/min.

Integumentary System

1. **Skin:**
   - Multiple large tense bulla are present over flexor aspect of forearms, groin, axilla, front and back of the trunk, some are on normal skin and some are on erythematous skin. Intact blisters contain clear fluid. Some bullae are ruptured. There are multiple denuded areas that do not increase by confluence. Most of the ruptured bullae are in healing stage and some are healed with mild hyperpigmentation.

- Erythematous patches are mostly observed over the trunk. Most of the lesions show central clearing.
- Nikolsky and Asboe-Hansen signs are negative.

2. **Hair:** Normal.
3. **Nail:** Normal.
4. **Mucous membrane:**
   - Conjunctival—normal.
   - Oral—normal.
   - Genital—normal.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 65 years old, retired police officer, normotensive, nondiabetic, nonsmoker, hailing from … presented with multiple blisters over different parts of the body for … months. The blisters at first appeared over forearms and gradually involved axilla, groin and front and back of trunk. Most of the blisters are large and tense, few are small. Some blisters have ruptured leaving denuded areas that have healed spontaneously. He also noticed erythematous patches over the front and back of the trunk, some of which healed spontaneously. There is no involvement of the mouth or genitalia.

The patient also complains of mild generalized itching for the same duration. He had similar attack 3 years back, but the lesions were sparse and recovered completely. He did not complain of difficulty in swallowing. There is no history of fever, joint pain, muscle pain or intake of any drugs prior to the appearance of these blisters. His bowel and bladder habits are normal.

On general examination – (mention as above).

On examination of the integumentary system – (mention as above).

Examination of other systems reveals no abnormalities.

My diagnosis is bullous pemphigoid.

Q. What are your **differential diagnoses?**

A. As follows:

- Pemphigus vulgaris
- Dermatitis herpetiformis
- Stevens Johnson syndrome
- Toxic epidermal necrolysis (TEN).

Q. What **investigations** do you suggest?

A. As follows:

1. Routine:
   - Complete blood count
   - Random blood sugar
   - Urine R/M/E.
2. Confirmatory:
   - Tzanck test
   - Skin biopsy for histopathology and DIF.

Q. How to **confirm** the diagnosis of bullous pemphigoid?

A. Skin biopsy for histopathology and direct immunofluorescence shows deposition of IgG and complement C3 at the basement membrane (in a linear pattern).

Histopathological findings are:

- Subepidermal bullae
- Absence of acantholysis
- Superficial dermal infiltration of many eosinophils.

Q. What are the **points in favor** and **against** your differential diagnoses?

A. As follows:

Differential diagnoses	Points if favor	Points against
1. Pemphigus vulgaris	» Bullae over the groin, axilla, trunk	» Bullae are large, tense » Ruptured bulla heals spontaneously » No mucous membrane involvement » Nikolsky and Asboe-Hansen signs are negative
2. Dermatitis herpetiformis	» Tense blisters over the forearms » Pruritus present » Mucous membranes are not involved	» Old age » Bullae and erythematous patches present, but lesions are not polymorphous

Q. How to **treat** bullous pemphigoid?

A. As follows:

1. General treatment: Bed rest, maintenance of electrolyte, adequate nutrition, etc.
2. Steroid:
   - Prednisolone 0.5 to 0.75 mg/kg/day, should be tapered slowly over few weeks after clinical improvement (may be required to continue for 2 to 3 years).
   - Potent topical steroid can be given alone.
   - In severe cases, methylprednisolone 15 mg/kg IV daily for 3 doses.
3. Tetracycline 500 mg 6 hourly with nicotinamide 500 mg 8 hourly.
4. Other drugs include dapsone, azathioprine, methotrexate, cyclophosphamide, cyclosporine and mycophenolate mofetil.
5. IV immunoglobulin.
6. Antihistamine, if needed.

Note

Bullous pemphigoid responds to lower dose of prednisolone.

RELATED QUESTIONS AND ANSWERS

Q. How do you **differentiate** pemphigus vulgaris from bullous pemphigoid?

A. As follows:

Points	Pemphigus vulgaris	Bullous pemphigoid
1. Age	Middle age (50 to 60 years)	Elderly (> 60 years), few in infants and children
2. Distribution	Scalp, face, flexures, may be generalized	Trunk, limb, flexures
3. Mucosa of mouth conjunctiva and genitalia	Commonly involved (60%)	Rarely involved (20%), oral mucosa is involved usually
4. Lesion	Intraepidermal flaccid bullae that rupture easily and has a less tendency to heal	Subepidermal, large, tense blisters that do not rupture easily and has a more tendency to heal Urticarial plaques, erythematous patches, papules and nodules may be found
5. Asboe-Hansen and Nikolsky signs	Positive	Negative
6. Target antigen	Desmoglein 3, sometimes desmoglein 1	BP 230 and BP 180
7. Antigens (κDa)	130 κDa and 160 κDa	230 κDa and 180 κDa
8. Direct immuno-fluorescence	Intercellular deposition of IgG and C3 in mosaic pattern (C3 only lesional)	Basement membrane deposition of IgG and C3 in linear pattern (C3 both lesional and non-lesional)
9. Treatment	Steroid with higher dose	Steroid with lower dose
10. Prognosis	Variable prognosis. May be fatal because of treatment complications and sepsis. Recurrence is common	Better prognosis. Does not affect general health. Usually self-limited over 5 to 6-year-period, may be fatal in very elderly person

Q. What is the **pathogenesis** of bullous pemphigoid?

A. IgG autoantibody binds to BP antigen in the lamina lucida. Complement is activated that produces factors with anaphylatoxic and chemotactic activity. Mast cells are activated and degranulated with the release of eosinophil chemotactic factors. Eosinophils accumulate in the dermis and adhere to the basement membrane. They release tissue destructive enzymes and reactive oxygen intermediates. Resultant injury to the zone causes dermoepidermal separation and blister formation.

Q. What are the **presentations** of pemphigoid?

A. It is common in the elderly, > 60 years. The patient presents with:

- Tense bullae, red urticarial patch, less rupture, with a tendency to heal, may be urticarial, mostly in trunk, limbs and flexures.
- Mouth involvement (rare, and in < 20%).

Note

Pemphigoid may be associated with lymphoma.

Q. What is the **site of lesion** in pemphigoid?

A. The lesion is in the basement membrane between epidermis and dermis **(subepidermal),** hence fewer tendencies to rupture.

Q. What are the diseases that cause **subepidermal bullae**?

A. The following diseases show subepidermal blister histopathologically:

- Bullous pemphigoid
- Dermatitis herpetiformis
- Herpes gestationis
- Linear IgA dermatosis
- Porphyria cutanea tarda
- Lichen planus
- Bullous SLE
- Lichen sclerosus atrophicus.

Q. What is **herpes gestationalis (pemphigoid gestationis)?**

A. It is the pregnancy-related skin lesions characterized by an itchy blistering urticated eruption that starts on the abdomen, often involving the umbilicus, and may become widespread. Large bullae may be present. It usually appears in the fifth or sixth month of pregnancy but may occur earlier, even in first trimester. It is a self-limited disease, but may recur in subsequent pregnancy. Diagnosis is confirmed by histology and immunofluorescence study. The blisters are eosinophil rich and subepidermal, with C3 in the basement membrane and serum complement-fixing immunoglobulin antibody. In mild case, topical corticosteroid is used but in severe case systemic steroid is needed. The dose may need to be increased after delivery as there is often a postpartum flare up of the disease. Oral contraceptive pills should be avoided, since they also flare up the disease. A transient bullous eruption occurs in 5% of infants, but there is no increase in fetal mortality.

Q. What are the diseases **associated** with bullous pemphigoid?

A. The following diseases are found to be associated with bullous pemphigoid:

- Diabetes mellitus
- Rheumatoid arthritis
- Dermatomyositis
- Ulcerative colitis
- Myasthenia gravis
- Thymoma.

Q. What are the **mechanisms** of blister formation?

A. Blisters are formed by the following mechanisms:

- Autoimmune mediated (dissolution of intracellular cement substance via acantholysis, e.g. pemphigus).
- Detachment of horny layer (subcorneal pustular dermatosis).
- Due to intracellular degeneration causing separation of cells from one another (e.g. friction blisters).
- Spongiotic blister due to intercellular edema (irritant contact dermatitis).
- Acantholysis due to ballooning degeneration (herpes simplex).
- Degeneration of basal cells causing loose contact with dermis (lichen planus).
- Degenerative changes in the basal membrane zone (bullous pemphigoid).

LICHEN PLANUS

CHIEF COMPLAINTS

- Multiple itchy papules in all extremities and over trunk for … months.

HISTORY

History of present illness: According to the statement of the patient, he was reasonably well … months back. Since then, he has been suffering from multiple violaceous papules that first involved the flexor aspect of forearms. The papules are extremely itchy. Gradually, there are also multiple papules that have involved the legs, thigh, arms and trunk. Some of the papules enlarged in size and turned into large plaques. After some days, the patient experienced the involvement of the nails and mouth cavity. There is no history of fever, joint pain, muscle pain or bleeding from any site. He did not take any drug prior to the lesions. His bowel and bladder habits are normal.

Past history

Family history

Personal history

Drug history: Mention according to the statement of the patient.

GENERAL EXAMINATION

- The patient is emaciated
- Mildly anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia, edema
- No lymphadenopathy or thyromegaly
- Pulse: 110/min
- Blood pressure: 110/70 mm of Hg
- Respiratory rate: 16/min
- Temperature: 98°F.

Integumentary System

1. **Skin:**
   - Inspection: There are bilateral symmetrical multiple flat-topped violaceous papules and plaques in both upper and lower extremities, more numerous in flexor aspect of forearms and shins. Koebner's phenomenon is seen in the extremities. Wickham's striae is present (mention if any).
   - Palpation: The papules are firm in consistency, nontender and not fixed to the underlying structure.
2. **Oral mucosa:** Violaceous, reticulate lesions on the inner aspect of cheeks, consisting of pinhead size silvery white papules.
3. **Nails** of ring and middle fingers of right hand show longitudinal ridging and grooving, also onycholysis involving ring and small fingers of the left hand.
4. **Hair** shows no abnormality.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 26 years old, businessman, nonsmoker, nondiabetic, hailing from …, presented with multiple violaceous papules that first involved the flexor aspect of forearms for … months. The papules are extremely itchy. Gradually, there are also multiple papules that have involved the legs, thigh, arms and trunk. Some of the papules enlarged in size and turned into large plaques. After some days, the patient experienced involvement of the nails and mouth cavity. There is no history of fever, joint pain, muscle pain or bleeding from any site. He did not take any drug prior to the lesions. His bowel and bladder habits are normal. There is no history of previous skin disease. For his present complaints, he was treated with some drugs by local doctors, but he could not remember the name.

On examination, general examination – mention as above.

Integumentary system – mention as above.

Examination of other systems shows no abnormalities.

My diagnosis is lichen planus.

Q. What investigations should be done in lichen planus?

A. As follows:

1. Routine:
   - Complete blood count
   - Viral marker for hepatitis B and C
   - Liver function tests and renal function tests for therapeutic purpose.
2. Specific: Skin biopsy for histopathology and DIF.

RELATED QUESTIONS AND ANSWERS

Q. Describe a **typical lesion** of lichen planus.

A. It is characterized by flat-topped, pruritic, polygonal violaceous papules on the flexors of wrist, trunk, medial aspect of thighs and shins. Wickham striae and Koebner phenomenon are present. Oral mucosa shows reticulated whitish (or violaceous) plaques consisting of pin head papules on the inner aspect of cheeks. Nail shows longitudinal grooving, proximal and distal onycholysis, ridging and splitting.

Q. What are the other **causes** of flat topped papules?

A. As follows:

- Lichen amyloidosis
- Lichen nitidus
- Lichen myxedematosus.

Q. What is the cause of **Wickham striae**?

A. It is because of focal increase in the thickness of granular layer and total epidermis. It is better seen with a hand lens (and by aniline dye).

Q. What are the **different types** of mucosal lesions?

A. As follows:

- Ulcerative—50%
- Reticulate—30%
- Atrophic—20%.

Q. What are the **drugs** that may cause lichenoid drug reactions?

A. Beta blockers, thiazides, spironolactone, frusemide, ACE inhibitors, calcium channel blockers, antimalarials, heavy metals, arsenic, lithium, iodides.

Q. What are the **types of lichen planus?**

A. As follows:

1. According to configuration:
   - Linear
   - Annular.
2. According to morphology of lesions:
   - Hypertrophic
   - Atrophic
   - Vesicobullous
   - Ulcerative and erosive
   - Actinic
   - Follicular
   - Lichen planus pigmentosus
   - Guttate and perforating.
3. According to site of involvement:
   - Lichen planus of the scalp
   - Mucosal lichen planus
   - Lichen planus of nails
   - Palmoplantar lichen planus
   - Inverse lichen planus in axilla, inframammary, groin, popliteal and antecubital areas.
4. Special variants:
   - Drug induced LP
   - Lichen planus and LE overlap
   - Lichen planus pemphigoides
   - Keratosis lichenoides chronica
   - Lichenoid reaction of graft versus host disease
   - Lichenoid keratosis
   - Lichenoid dermatitis.

Q. What are the **differences** between lichen planus and lichen nitidus?

A. As follows:

Points	Lichen planus	Lichen nitidus
1. Size	Variable, usually large	1 to 2 mm
2. Shape	Polygonal	Round
3. Color	Erythematous to violaceous	Shiny, discrete
4. Wickham striae	Present	Absent
5. Pruritus	Marked	Uncommon
6. Mucosal change	Frequently present	Rare

Q. What are the **differences** between lichenoid drug reaction and lichen planus?

A. As follows:

Points	Lichenoid drug reaction	Lichen planus
1. Site	Sun exposed areas	Flexor areas
2. Lesions	Larger and scaly	Smaller
3. Wickham striae	Absent	Present
4. Alopecia	More	Less
5. Mucosal involvement	Less	More

Q. What are the **differential diagnoses** of lichen planus?

A. Differential diagnosis of lichen planus depends on type:

1. Hypertrophic:
   - Lichen simplex chronicus
   - Psoriasis
   - Lichen amyloidosis.
2. Annular:
   - Granuloma annulare
   - Annular syphilis
   - Annular psoriasis.
3. Linear:
   - Lichen striatus
   - Linear morphea.
4. Atrophic:
   - Lichen sclerosus atrophicus
   - DLE.
5. Guttate:
   - Guttate psoriasis
   - Pityriasis rosea.
6. Oral:
   - Candidiasis
   - Secondary syphilis.
7. Follicular:
   - Lichen spinulosus
   - Lupus erythematosus.

Q. What are the histopathological and DIF findings in lichen planus?

A. As follows:

- Histopathology shows—hyperkeratosis, beaded hypergranulosis and saw tooth pattern of epidermal hyperplasi**.** There is destruction of basal layer that is squamatized. In superficial dermis, there is dense band like infiltrate of lymphocytes and melanophages. Civatte bodies represent necrotic keratinocytes.
- DIF shows—clumps of IgM and less frequently IgA, IgG and C_3 subepidermally corresponding to civatte bodies.

Q. How to treat lichen planus?

A. Treatment depends according to the type and extent of the disease:

1. General measures:
   - Avoid drugs, such as diuretics, beta blockers, antimalarials
   - Protection from trauma.

2. Cutaneous lesions:
   - First line:
     - Topical –
       - Topical steroids
       - Intralesional
       - Tacrolimus
       - Pimecrolimus.
     - Physical – Psoralen and ultraviolet light
     - Systemic –
       - Systemic steroid – Prednisolone 30 to 80 mg/day
       - Etretinate 10 to 75 mg/day
       - Acitretin 30 mg/day
       - Isotretinoin 20 to 40 mg/day.
   - Second line:
     - Cyclosporine 3 to 10 mg/kg/day
     - Dapsone 200 mg/day
     - Hydroxychloroquine 200 to 400 mg/day
     - Azathioprine 50 mg bid
     - Mycophenolate mofetil 1500 mg bid.
3. Oral lesions:
   - Topical steroid in orabase, nystatin with clobetasol, topical tretinoin with steroid, 1% topical tacrolimus.
   - PUVA and 308 nm excimer laser.
   - Systemic—hydroxychloroquine 200 mg to 400 mg daily for 6 months. Thalidomide 150 mg/day.
   - Other agents used in cutaneous lesions also improve oral lesions.
4. Special forms:
   - Doxycycline, tetracycline and nicotinamide—LP pemphigoides
   - Interferon α and β generalized
   - Metronidazole generalized
   - Cyclophosphamide—refractory LP
   - Methotrexate—refractory LP.

Q. What is the course or prognosis of lichen planus?

A. Two-third of patients will have lichen planus of less than 1 year. Many patients cure spontaneously within 1 year. Recurrence occurs in half of the patients.

Q. What are the medical causes of itching?

A. As follows:

1. Liver disease—primary biliary cirrhosis, obstructive jaundice
2. Chronic renal failure
3. Hematological—polycythemia rubra vera (after warm bath), lymphoma (especially Hodgkin's disease), leukemia, multiple myeloma, iron deficiency anemia
4. Endocrine cause—hypothyroidism, thyrotoxicosis, diabetes mellitus (especially associated with candidiasis).
5. Any internal malignancy
6. HIV
7. Psychogenic.

Q. What are the **dermatological manifestations of internal malignancy**?

A. As follows:

- Dermatomyositis—bronchial carcinoma, malignancy of GIT, genitourinary.
- Acanthosis nigricans—may be found in malignancies of GIT, lung, liver.
- Paget's disease of nipple—ductal carcinoma of breast.
- Erythroderma—lymphoma, leukemia.
- Tylosis—esophageal carcinoma.
- Ichthyosis—lymphoma.
- Erythema gyratum repens (concentric rings of erythema)—malignancies of lung, breast.
- Necrolytic migratory erythema (burning, geographic and spreading annular areas of erythema) —glucagonoma.

ARSENICOSIS

CHIEF COMPLAINTS

- Multiple hyper and hypopigmented lesions in different parts of the body for … months
- Thickening and pigmentation of the palms and soles for … months
- Nausea, vomiting and weight loss for … months.

HISTORY

History of present illness: According to the statement of the patient, he was reasonably well … months back. Since then, he has observed numerous hyper and hypopigmented lesions in different parts of the body that first appeared on the trunk and then gradually involved the rest of the body. These are painless, non-itchy and not associated with any loss of sensation. For the last … months, he has noticed gradual thickening and pigmentation of the palms and soles that are painless and non-itchy. The patient also complains of nausea and occasional vomiting for … days that is not related to intake of food. There is no difficulty in deglutition. He also complains of loss of appetite, substantial weight loss, constipation and progressive weakness. His bladder habit is normal. There is no history of fever, cough, muscular pain or joint pain.

Past history

Family history

Personal history

Socioeconomic history: The patient used to drink water from tubewell for long time. Recently, it has been marked red due to high arsenic level. Now, he drinks water from arsenic free tubewell.

Drug history: Mention according to the statement of the patient.

GENERAL EXAMINATION

- The patient looks emaciated
- Mildly anemic
- No jaundice, cyanosis, clubbing, koilonychia, leukonychia, edema
- No lymphadenopathy or thyromegaly
- Pulse: 105/min
- Blood pressure: 110/65 mm of Hg
- Respiratory rate: 16/min
- Temperature: 98°F.

Integumentary System

1. **Skin:**
   - There are multiple hyperpigmented lesions involving both upper and lower limbs and trunk with scattered hypopigmented area giving rise to rain drop appearance.
   - Multiple hard papular and plaque like lesions with hyperpigmentation are seen over the front of the chest.
   - There is hyperkeratosis of palms and soles.

2. **Oral mucosa:** Normal.
3. **Nails** are brittle. Some has transverse white striae (Mee's line).
4. **Hair** is dry and spars.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 56 years old, farmer, nonsmoker, nondiabetic, hailing from …, presented with numerous hyper and hypopigmented lesions on different parts of the body for … months. These first appeared on the trunk and then gradually involved the rest of the body. These are painless, non-itchy and not associated with any loss of sensation. For the last … months, he has noticed gradual thickening and pigmentation of the palms and soles that are painless and non-itchy. The patient also complains of nausea and occasional vomiting for … days that is not related to intake of food. There is no difficulty in deglutition. He also complains of loss of appetite, substantial weight loss, constipation and progressive weakness. His bladder habit is normal. There is no history of fever, cough, muscular pain or joint pain. The patient used to drink water from a tubewell for a long time that was recently marked in red due to high arsenic concentration.

On examination, general examination – mention as above.

Integumentary system – mention as above.

Examination of other systems shows no abnormalities.

My diagnosis is arsenicosis (or chronic arsenic toxicity).

Q. What are your **differential diagnoses**?

A. As follows:

- Hemochoromatosis
- Lepromatous leprosy
- Tinea versicolor
- Addison's disease.

Q. What **investigations** are done in chronic arsenic toxicity?

A. As follows:

1. Routine:
   - FBC
   - Urine for routine examination
   - Chest X-ray
   - Liver function tests
   - Renal function tests
   - ECG
   - EEG
   - Nerve conduction test
2. Confirmatory—Measurement of arsenic concentration in hair, nail, urine and serum.

Q. How to **confirm** chronic arsenic poisoning?

A. By measuring the arsenic concentration in hair, nail, urine and serum.

Normal value of arsenic:

- Blood < 3 mg/L (or 5 to 50 ppb/mg/L)
- Urine 0.005 to 0.04 mg/L

- Hair 0.08 to 0.25 mg/kg (pubic hair is preferred due to lack of contamination)
- Nail 0.43 to 1.08 mg/kg
- Daily urinary excretion < 0.1 mg/L.

Note Remember the following points

- Skin manifestations require 1 year to develop
- Systemic manifestations require 10 years to develop
- Early signs of arsenic toxicity—conjunctivitis, transient icterus and hyperhidrosis.

RELATED QUESTIONS AND ANSWERS

Q. What is the **mechanism** of arsenic toxicity?

A. After absorption, arsenic is widely distributed to all the tissues of body. It combines with sulfhydryl-containing substances and inhibits the activity of many enzymes. It interferes with cell enzymes, cell respiration and mitosis.

Q. What are the **clinical presentations** of arsenicosis?

A. As follows:

- Melanosis—hyperpigmentation (generalized or localized) with few scattered hypopigmented areas giving raise to **raindrop** appearance.
- Hyperkeratosis of mainly palm and sole. May be multiple, punctate, hard, discrete, papule and verrucous plaque.
- Nails—brittle, may show transverse white striae of finger nails **(Mees' line).**
- Hair—dry, may fall off.
- Eye—conjunctivitis.
- Nose—rhinitis, epistaxis, nasal obstruction and septal perforation.
- It may involve any system of the body (liver, kidney, lung and heart).

Q. What are the **diagnostic signs** of arsenicosis?

A. As follows:

- Hyperkeratosis of palms and soles
- Hyperpigmentation and hypopigmentation (on trunk and extremities) are the hallmarks.

Q. What are the **systemic effects** of chronic arsenic toxicity?

A. As follows:

1. GIT: Anorexia, nausea and vomiting.
2. Hepatic: Hepatomegaly, cirrhosis of liver and noncirrhotic portal hypertension.
3. Central nervous system (CNS): Peripheral neuropathy, seizure, confusion and encephalopathy.
4. Hematological: Anemia, leukopenia and thrombocytopenia.
5. Musculoskeletal: Myalgia, arthralgia and atrophy of extensor muscles causing wrist drop or foot drop.
6. Renal: Dysuria, anuria and renal tubular necrosis.
7. Heart: Cardiomyopathy, arrhythmia and heart failure.
8. Vascular: Peripheral vascular insufficiency causing black foot disease.
9. Endocrine: Diabetes mellitus may be precipitated.
10. Malignancy:
    - Skin—squamous cell carcinoma, basal cell carcinoma and Bowen's disease.
    - Carcinoma of lung, kidney, urinary bladder, liver (angiosarcoma), prostate and colon.

Q. How to **treat** chronic arsenic toxicity?

A. As follows:

1. Drinking of arsenic contaminated water must be stopped.
2. High protein diet.
3. Antioxidant (vitamin A 50,000 IU, vitamin C 500 mg and vitamin E 200 mg daily for 3 months).
4. Vitamins and minerals supplement.
5. Vegetables and fresh fruits.
6. *Spirulina* (an algae), which is rich in high protein, may help to clear arsenic.
7. For skin lesion: Keratolytic emollients (salicylic acid, urea and retinoic acid), cryotherapy, electrocautery and laser therapy.
8. Drugs (chelating agent may be used):
   - D-penicillamine (250 mg TDS) for 3 months, or
   - Dimercaprol (BAL), dimercaptosuccinic acid (DMSA) and dimercaptopropane sulfonate (DMPS). BAL has a tendency to redistribute arsenic to brain and testes. DMSA and DMPS are more preferable, because of their low toxicity.

Dose:

- DMSA—10 mg/kg/day for 7 days followed by 10 mg/kg/day three times for 14 days.
- DMPS—100 mg TDS to QDS for every alternate week for three courses.

Preventive therapy: Drinking water should be safe.

Q. What are the **differential diagnoses** of arsenicosis?

A. As follows:

1. For pigmentation:
   - Lepromatous leprosy
   - Hemochromatosis
   - Addison's disease
   - Xeroderma pigmentosum
   - Guttate psoriasis
   - Tinea versicolor
   - Idiopathic guttate hypomelanosis
   - Postinflammatory hypopigmentation and hyperpigmentation
   - Drug melanosis.

2. For keratosis:
   - Epidermodysplasia verruciformis
   - Multiple corn or callosities
   - Verruca vulgaris
   - Hereditary palmoplantar keratoderma
   - Acrokeratosis verruciformis.

LEG ULCER (VENOUS ULCER)

CHIEF COMPLAINTS

- Swelling of both legs for … years
- Gradual darkening of skin on both legs for … months
- Appearance of an ulcer on the inner aspect of right lower leg for … days.

HISTORY

History of present illness: The patient states that he was reasonably well … years back. Since then, he has been suffering from swelling of both legs. This is more marked during the evening, disappears in the morning and also occasionally after prolonged lying. For the last … months, the patient also complains of gradual darkening of his feet and lower legs, followed by an itchy, oozing lesion that became ulcerated on the inner aspect of his right lower leg. The ulcer is slightly painful with oozing, but no bleeding and there is no sign of healing. He did not give any history of blister before ulceration (to differentiate from pyoderma gangrenosum) or any rash. The patient agreed that he has to stay standing for a long time due to his occupation as a policeman.

He did not give any history of trauma, tingling or numbness of his toes, loss of sensation, muscular weakness, joint pain, pain on back of legs while walking, fatigue or weakness, loss of hair or reduced temperature. The swelling of the legs are not associated with breathlessness, cough, chest pain, palpitation, jaundice or any urinary complaint. His bowel and bladder habits are normal.

History of past illness: He is not diabetic or hypertensive. He is suffering from varicose vein for the last … years.

Family history: Nothing significant.

Personal history: He is a nonsmoker.

Drug and treatment history: He was treated with local and oral antibiotics, antihistamines and furosemide.

Socioeconomic condition: He drinks arsenic free water from a tubewell.

GENERAL EXAMINATION

- The patient looks normal
- No anemia, jaundice, cyanosis, clubbing, koilonychia, leukonychia
- Bilateral pitting edema present
- No lymphadenopathy or thyromegaly
- Pulse: 110/min. All the peripheral pulses are present
- Blood pressure: 120/70 mm of Hg
- Respiratory rate: 16/min
- Temperature: 98ºF.

Examination of lower limbs:

- **Skin:** There are pin-pointed hyperpigmented macules and patches involving both lower legs and feet with crusted, oozing plaque on medial aspect of left leg. There is a solitary ulcer over the right medial malleoli, 4 cm × 2 cm in diameter, margin is irregular, floor is clear, base is tender but no oozing. Surrounding skin is pigmented and warm.

- There are bilateral varicose veins, of variable size and shape.
- All the peripheral pulses are present. There is no pallor on elevation or redness of the foot on lowering the leg (dependent rubor).
- **Hair:** Normal.
- **Nail:** Normal.

Mucous membrane: Normal.

Conjunctiva: Normal.

Genitalia: Normal.

Nervous system: No sensory or motor impairment in both lower limbs.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURE

Mr …, 45 years old, a policeman, normotensive, nondiabetic, nonsmoker, hailing from …, presented with swelling of both legs for … months. This is more marked during the evening, disappears in the morning and also occasionally after prolonged lying. For the last … months, the patient also complains of gradual darkening of his feet and lower legs, followed by an itchy, oozing lesion that became ulcerated on the inner aspect of his right lower leg. The ulcer is slightly painful with oozing, but no bleeding and there is no sign of healing. He did not give any history of blister before ulceration (to differentiate from pyoderma gangrenosum) or any rash. The patient agreed that he has to stay standing for a long time due to his occupation as a policeman.

He did not give any history of trauma, tingling or numbness of his toes, loss of sensation, muscular weakness, joint pain, pain on back of legs while walking, fatigue or weakness, loss of hair or reduced temperature. The swelling of the legs are not associated with breathlessness, cough, chest pain, palpitation, jaundice or any urinary complaint. His bowel and bladder habits are normal. He is suffering from varicose vein for the last … years. He was treated with local and oral antibiotics, antihistamines and frusemide.

General examination (as above).

Examination of integumentary system (as above).

Examination of the other systems reveals no abnormalityies.

My diagnosis is venous ulcer.

Q. Why not this is arterial ulcer?

A. Usually arterial ulcer is more on the lateral surface of the ankle or on the distal digits. It is usually tender, punched-out with cold skin, loss of hair, and absent or reduced pulse. There may be dry gangrene.

Q. What are the other causes of leg ulcer?

A. As follows:

1. If the patient is elderly, probable causes are:
   - Trauma
   - Atherosclerosis
   - Diabetes mellitus
   - Tuberculosis

- Leprosy
- Leishmaniasis.

2. If the patient is younger, probable causes are:
   - Trauma
   - Diabetes mellitus
   - Hematological disease (thalassemia, hereditary spherocytosis)
   - Collagen disease (SLE, rheumatoid arthritis).

Q. What **investigations** should be done in leg ulcer?

A. As follows:

- Hb%, TC, DC and ESR
- Blood sugar
- Lipid profile (in atherosclerosis)
- Pus (if any), for C/S, AFB, LD bodies
- Doppler USG of lower limb vessels
- X-ray of leg (calcification in artery may be seen)
- Arteriography
- Biopsy
- Others—according to suspicion of causes, e.g. ANF, cold agglutinin and RA test.

Q. What are the **causes** of leg ulcer?

A. As follows:

1. Traumatic.
2. Infection (pyogenic, lupus vulgaris, leprosy, cutaneous leishmaniasis, sporotrichosis, blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, schistosomiasis, late gummatous syphilis).
3. Arterial causes are atherosclerosis, peripheral vascular disease (including Buerger's disease, Raynaud's disease, etc.) and arterial occlusion. Arterial ulcer (or ischemic ulcer) occurs more on the lateral surface of the ankle or the distal digits. It is usually tender, punched-out with cold skin, loss of hair, and absent or reduced pulse. There is pallor on elevation and redness of foot on lowering the leg (dependent rubor). There may be dry gangrene.
4. Venous ulcer occurs usually due to varicose vein. It is common around malleoli or in medial side. The leg is edematous. There may be wet gangrene, pigmentation, eczema, lipodermatosclerosis (combination of induration, reddish brown pigmentation and inflammation—a fibrosing panniculitis of the subcutaneous tissue) and scarring white atrophy with telangiectasia (atrophie blanche).
5. Neuropathic ulcer occurs in diabetes mellitus, tabes dorsalis, syringomyelia, leprosy, polyneuropathy due to any cause. This type of ulcer is usually painless and more on the plantar surface of foot, callosities and pressure points. There is impaired sensation on the affected part.
6. Collagen diseases, such as SLE, rheumatoid arthritis, Felty's syndrome, cryoglobulinemia, polyarteritis nodosa, etc.
7. Hematological diseases, such as sickle cell anemia, thalassemia, hereditary spherocytosis, paroxysmal nocturnal hemoglobinuria, thrombotic thrombocytopenic purpura and macroglobulinemia.
8. Neoplastic disorders, such as squamous cell carcinoma, basal cell carcinoma, lymphoma and Kaposi's sarcoma.
9. Miscellaneous: Pyoderma gangrenosum, dermatitis artefacta, drugs.

Q. How to **treat** leg ulcer?

A. As follows:

1. General measures:

- Smoking should be stopped
- Control of DM, hypertension, obesity (if any)
- Treatment of primary cause
- Local care (cleaning and dressings).

2. Specific measures:
   - Antibiotic, if any infection
   - Low dose aspirin
   - In some cases, surgery (balloon dilatation) and if necessary, amputation
   - Consult with chiropodist.

LEUKOCYTOCLASTIC VASCULITIS (SMALL VESSEL VASCULITIS)

CHIEF COMPLAINTS

- Multiple painful pigmented elevated lesions on upper and lower extremities for 3 weeks.
- Joint pain and leg edema for 3 weeks.
- Fever for 1 week.

HISTORY

History of present illness: According to the patient, she was reasonably well 3 weeks ago. Since then, she has noticed multiple painful pigmented elevated lesions on her upper and lower limbs including buttocks. The lesions first appeared on the legs and then gradually spread to other sites including palm and soles. The lesions showed progressive color change from red to dark pigmented and smaller pigmented lesions coalesces to form larger lesions. There is no itching, burning, discharge or exfoliation from the lesions. She also complains of pain in large and small joints of upper and lower limbs without any swelling. She also noticed swelling of both feet and ankles for 3 weeks. There is no variation in swelling throughout the day. She did not give any history of medication, throat pain, abdominal pain, bloody diarrhea, gum bleeding, oral ulcer, photosensitivity, hair loss, high color urine, cough, chest pain, hemoptysis, shortness of breath, jaundice. She also complains of low grade continued fever without any chill, rigor or sweating.

History of past illness:

Family history

Personal history

Drug and treatment history: She was treated by some local doctors by some painkillers, the name of which she cannot mention.

Socioeconomic condition

GENERAL EXAMINATION

- The patient looks normal
- No anemia, jaundice, cyanosis, clubbing, koilonychia, leukonychia
- Bilateral pitting edema present
- No lymphadenopathy or thyromegaly
- Pulse: 110/min. All the peripheral pulses are present
- Blood pressure: 120/70 mm of Hg
- Respiratory rate: 16/min
- Temperature: 98ºF.

Integumentary System

- **Skin:** There are multiple purpura that are painful, palpable, some are erythematous and some are hyperpigmented, involving both upper and lower extremities including palm and soles. There is no ulceration, ecchymosis, nodules, plaques, urticaria or scarring.
- **Hair:** Normal.
- **Nail:** Normal.

- **Mucous membrane:** Normal.
- **Conjunctiva:** Normal.
- **Genitalia:** Normal.

Joints

- Grade 1 tenderness involving the ankles, knees, wrists, elbows and small joints of the hands. There is no swelling.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURE

Ms …, 20 year old, student, normotensive, nondiabetic, nonsmoker, hailing from …, presented with multiple painful pigmented elevated lesions on her upper and lower limbs including buttocks for 3 weeks. The lesions first appeared on the legs and then gradually spread to other sites including palm and soles. The lesions showed progressive color change from red to dark pigmented and smaller pigmented lesions coalesces to form larger lesions. There is no itching, burning, discharge or exfoliation from the lesions. She also complains of pain in large and small joints of upper and lower limbs without any swelling. She also noticed swelling of both feet and ankles for 3 weeks. There is no variation in swelling throughout the day. She did not give any history of medication, throat pain, abdominal pain, bloody diarrhea, gum bleeding, oral ulcer, photosensitivity, hair loss, high color urine, cough, chest pain, hemoptysis, shortness of breath, jaundice. She also complains of low grade continued fever without any chill, rigor or sweating. She was treated by some local doctors by some painkillers, the name of which she cannot mention.

General examination (as above).

Examination of integumentary system (as above).

Examination of the other systems reveals no abnormalities.

My diagnosis is idiopathic cutaneous small vessel vasculitis (leukocytoclastic vasculitis).

Q. What are your **differential diagnoses?**

A. As follows:

- Henoch Schonlein purpura
- Urticarial vasculitis
- Connective tissue disease (such as SLE, rheumatoid arthritis)
- Microscopic polyangiitis
- Churg Strauss syndrome
- Wegener's granulomatosis
- Cryoglobulinemic vasculitis
- Polyarteritis nodosa
- Lymphoma (HD).

Q. What **investigations** do you suggest in this patient?

A. As follows:

1. Routine:
   - CBC, platelet count, PBF
   - Urine R/M/E
   - X-ray chest.

2. To exclude other cause:
   - Throat culture and ASO titer
   - Hepatitis B and C serology
   - ANA, anti-ds-DNA
   - RA test, RW test, Anti-CCP antibody
   - pANCA, cANCA
   - Serum complement.
3. Specific: Skin biopsy with DIF (perilesional in case of Henoch Schonlein purpura).

Q. What are the **biopsy** findings?

A. As follows:

- There is angiocentric segmental inflammation of the postcapillary venule with expansion of the vessel wall, fibrin deposition, and infiltration by neutrophils that show fragmentation of their nuclei (karyorrhexis or leukocytoclasia).
- Endothelial cell swelling is common, may be endothelial necrosis in serious illness (including septic vasculitis, ANCA associated vasculitis).

Q. What are the **DIF** findings?

A. As follows:

- Immunoglobulins, complement components and fibrin deposits within postcapillary venule walls if the biopsy is taken within the first 24 hours.
- Later, fibrin is prominent but immunoglobulin deposits may be absent. But, in Henoch Schonlein purpura, there is prominent IgA deposit even in more advanced lesions.

Q. What is **leukocytoclastic vasculitis** (LCV)?

A. It is the most common cutaneous small vessel vasculitis. Usually there is symmetrical palpable purpura involving the lower legs. Systemic involvement is rare. It may be caused by drugs, infection, inflammatory disease or malignant disease, but often no cause is found (55 to 60%). Investigations are only necessary with persistent lesions or associated signs and symptoms. It often resolves spontaneously, but treatment with analgesia, support stockings, dapsone or prednisolone may be needed to control the pain and to heal up any ulceration.

Q. What is the pathogenesis of **cutaneous small vessel vasculitis**?

A. Cutaneous small vessel vasculitis is due to circulating immune complexes, which involves the vessel walls and activate complement. Various inflammatory mediators are produced, contributing to endothelial injury.

Q. What are the **treatments** of cutaneous small vessel vasculitis?

A. Most of the cases are acute, self-limiting and do not involve the internal organ. In such cases, the following measures should be taken:

1. General measures:
   - Rest and elevation of the legs
   - Avoidance of trauma and cold
   - Analgesics, for pain
   - Treatment of the primary cause, if any.
2. If the disease is limited to the skin, colchicines 0.6 mg 2 to 3 times daily or dapsone 50 to 200 mg/day for 2 to 3 weeks.
3. In severe, intractable or recurrent case or if there is internal organ involvement:
   - Systemic corticosteroid (prednisolone 60 to 80 mg/day).
   - In refractory case, immunosuppressive agents, such as mycophenolate mofetil 2 to 3 g/day, methotrexate 5 to 25 mg/week, azathioprine 50 to 200 mg/day may be given.

- In more difficult cases, cyclophosphamide, monthly intravenous pulse corticosteroid or cyclophosphamide, cyclosporine 3 to 5 mg/kg/day may be given.
- TNF-α blockers like infliximab may be used.

Q. What is **vasculitis**?

A. Inflammation of the vessel walls is called vasculitis.

Q. What is the **classification** of vasculitis?

A. As follows:

1. Cutaneous small vessel (postcapillary venule):
   a. Idiopathic cutaneous small vessel vasculitis:
   b. Henoch Schonlein purpura
   c. Acute hemorrhagic edema of infancy
   d. Urticarial vasculitis
   e. Cryoglobulinemic vasculitis
   f. Erythema elevatum diutinum
   g. Granuloma faciale
   h. Other disease with leukocytoclastic vasculitis: Drug induced vasculitis, malignancy (lymphoreticular more common than solid tumor), connective tissue diseases, hyperglobulinemic purpura, inflammatory bowel disease, bowel associated dermatitis arthritis syndrome (bowel bypass), HIV infection and neutrophilic dermatoses (Behcet's syndrome, Sweet syndrome, erythema nodosum leprosum, septic vasculitis, autoinflammatory disease—familial Mediterranean fever, serum sickness).
2. Medium vessel:
   a. Polyarteritis nodosa:
      - Benign cutaneous forms
      - Systemic form.
   b. Kawasaki's disease.
3. Mixed size (medium and small) vessel disease:
   a. Connective tissue disease associated (usually rheumatoid vasculitis)
   b. Septic vasculitis
   c. ANCA associated:
      - Microscopic polyangiitis
      - Wegener's granulomatosis
      - Allergic granulomatosis (Churg-Strauss syndrome)
      - Drug induced (most are post capillary venule only).
4. Large vessel vasculitis:
   a. Giant cell arteritis.
   b. Takayasu's arteritis.

ERYTHEMA NODOSUM

CHIEF COMPLAINTS

- Multiple reddish painful lesions over front of both legs for … days
- Pain in multiple joints for … week
- Dry cough for … weeks.

HISTORY

History of present illness: According to the patient he was reasonably well … days ago. Since then, he noticed multiple nodules of variable size and shape, present over the front of both lower legs. The nodules are painful, some are red and some are purple in color. He also complains of pain in knees, right ankle, right elbow and right wrist joints for … weeks, but there is no swelling. The patient has dry cough for … weeks, which is not associated with breathlessness or chest pain. There is no diurnal variation. It is not associated with exertion or exposure to allergens. He did not complain of any fever, sore throat. His bowel and bladder habits are normal.

History of past illness

Family history

Personal history

Drug and treatment history: He did not take any drugs prior to this illness. For the present complains, he took some cough syrup and analgesics but could not mention the names.

Socioeconomic condition: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient looks ill
- No anemia, jaundice, cyanosis, clubbing, koilonychia, leukonychia
- Bilateral pitting edema present
- No lymphadenopathy or thyromegaly
- Pulse: 92/min. All the peripheral pulses are present
- Blood pressure: 130/70 mm of Hg
- Respiratory rate: 18/min
- Temperature: 98ºF.

Integumentary System

- **Skin:** There are multiple nodular, tender lesions of variable size and shape, some are red and some are pigmented in the right or left or both shin.
- **Hair:** Normal.
- **Nail:** Normal.
- **Mucous membrane:** Normal.
- **Conjunctiva:** Normal.
- **Genitalia:** Normal.

Gastrointestinal Tract

- **Throat:** Normal
- **Liver:** Not palpable
- **Spleen:** Not palpable.

Examination of the other systems reveals no abnormalities.

SALIENT FEATURE

Mr …, 23 years old, student, normotensive, nondiabetic, nonsmoker, hailing from …, presented with multiple nodules of variable size and shape, present over the front of both lower legs for … days. The nodules are painful, some are red and some are purple in color. He also complains of pain in knees, right ankle, right elbow and right wrist joints for … weeks, but there is no swelling. The patient has dry cough for … weeks, which is not associated with breathlessness or chest pain. There is no diurnal variation. It is not associated with exertion or exposure to allergens. He did not complain of any fever, sore throat. His bowel and bladder habits are normal. He did not take any drugs prior to this illness. For the present complaints, he took some cough syrup and analgesics but could not mention the names.

General examination (as above).

Examination of integumentary system (as above).

Examination of the other systems reveals no abnormalities.

My diagnosis is erythema nodosum.

Q. What are your **differential diagnoses**?

A. As follows:

- Drug rash
- Erythema multiforme
- Purpura
- Cellulitis
- Erythema induratum
- Others: Nodular panniculitis, meningococcal septicemia, vasculitis (SLE and PAN).

Q. What **investigations** are done in erythema nodosum?

A. As follows:

- CBC, ESR, PBF (leukocytosis in streptococcal infection, high ESR in TB).
- Anti-streptolysin O (ASO) titer, throat swab for C/S, blood for C/S (in streptococcal infection).
- Chest X-ray (TB and sarcoidosis).
- Mantoux test (MT) and sputum for AFB (in case of TB).
- Lymph node FNAC and/or biopsy (sarcoidosis, lymphoma and TB).
- Inflammatory bowel disease (double contrast barium enema, sigmoidoscopy or colonoscopy, barium follow through).
- Other investigations: According to suspicion of cause.

RELATED QUESTIONS AND ANSWERS

Q. What is **erythema nodosum**? What are the **histological findings**?

A. It is an inflammatory disorder characterized by non-suppurative, painful, palpable, tender, erythematous nodular lesion in the skin, common in shin below the knee.

Usually, associated with fever, malaise and arthralgia. Nodules may be 2 to 6 cm in diameter, occur in crops, over 2 weeks, then resolves slowly over months leaving a bruise staining in the skin. It never ulcerates, may be recurrent and common in adult female.

Microscopy: Panniculitis (inflammatory reaction in fat), infiltration of lymphocytes, histiocytes, multinucleated giant cells and eosinophils, immune-complex deposition in dermal vessels.

Q. What are the **causes** of erythema nodosum?

A. As follows:

- Acute sarcoidosis
- Streptococcal β-hemolyticus infection (in throat)
- Primary pulmonary tuberculosis
- Drugs (sulfonamide, penicillin, estrogen-containing oral contraceptive pill, salicylates, barbiturates, sulfonylureas, bromides and iodides)
- Inflammatory bowel disease (Crohn's disease, ulcerative colitis)
- Fungal infections (histoplasmosis, coccidioidomycosis and blastomycosis, and is common in the USA)
- Protozoal (toxoplasmosis)
- Leprosy (erythema nodosum leprosum (ENL))
- Idiopathic (up to 50% cases)
- Physiological: Pregnancy (often unilateral).
- Others: *Salmonella*, *Shigella*, *Yersinia*, brucellosis, *Chlamydia*, rickettsial and mycoplasma infection, viral infection, lymphoma, cat-scratch disease, Behçet's syndrome and SLE.

Q. How to **treat** erythema nodosum?

A. As follows:

- Rest
- NSAIDs (indomethacin)
- Treatment of primary cause (e.g. penicillin, if streptococcal infection)
- In severe cases, corticosteroid should be given. In some cases dapsone 100 mg daily, colcichine 500 mg twice daily may be helpful
- Potassium iodide 400 to 900 mg daily may be helpful.

Q. What is **Erythema induratum (Bazin's disease)**?

A. Erythema induratum of Bazin type is a nodular vasculitis (which is a multifactorial syndrome of lobular panniculitis), related to tuberculous origin. It is one of the sequelae of immunologic reactions against antigenic components of *Mycobacterium tuberculosis* that spreads through blood. It represents a delayed type hypersensitivity reaction to tubercle bacillus. Recently, hepatitis C virus has been suspected as a cause. It is more common in women, aged 20 to 30 years, mostly occurring in lower extremities, usually in calves, may also be in shins. Differential diagnoses are chilblain, erythema nodosum, erythema nodosum leprosum, pancreatic panniculitis, lupus panniculitis, etc. Diagnosis is based on routine blood count, ESR, PCR and biopsy of the involved tissue. Treated with antituberculous therapy. Steroid may be indicated. Potassium iodide is sometimes needed for local application. Complication of untreated or inadequately treated erythema induratum involves persistent ulceration. If treated properly, the prognosis is good.

Q. What are the **differences** between erythema nodosum and erythema induratum?

A. As follows:

Points	Erythema nodosum	Erythema induratum
1. Duration	Short	Long
2. Site	Shin	Calf
3. Occurrence	Lesions occur simultaneously	Lesions occur serially in crops
4. Ulceration	Absent	Present
5. Pain	More	Less
6. Scarring	Absent	Present
7. Cause	Multiple causes	Usually TB
8. Histology	Septal panniculitis	Lobular panniculitis

CHAPTER 12

Miscellaneous

- Kala-azar 777
- Pyrexia of Unknown Origin (PUO) 785
- Takayasu's Disease 790
- PUO (HIV/AIDS) 793

KALA-AZAR

CHIEF COMPLAINTS

- Fever for ... months
- Loss of weight for … months
- Heaviness in left upper abdomen for … months
- Blackening of skin for ... months.

HISTORY

History of present illness: According to the statement of the patient, he was alright … months back. Since then, he has been suffering from fever, which is intermittent in nature, persists for 2 to 3 hours, subsides spontaneously, again reappears, 2 to 3 times daily. There is no history of chill or rigor, or any sweating. The patient also complaints of substantial loss of weight over last … months despite good appetite. There is no history of diarrhea, vomiting or urinary abnormality. He also complains of heaviness in left upper abdomen and fullness after taking food. For the last ... months, he also noticed blackening of skin involving the whole body. There is no history of cough, hemoptysis, hematemesis, melena or any other bleeding manifestation.

History of past illness: Mention according to the patient's statement.

Family history: Mention according to the patient's statement.

Personal history: Mention according to the patient's statement.

Drug history: The patient took paracetamol and some antibiotic prescribed by local physician the name of which he cannot mention.

GENERAL EXAMINATION

- The patient is emaciated.
- There is generalized pigmentation.
- Moderately anemic.
- No cyanosis, jaundice, edema, clubbing, koilonychias or leukonychia.
- No lymphadenopathy or thyromegaly.
- Pulse: 120/min.
- BP: 90/70 mm Hg.
- Temperature: 99ºF.

SYSTEMIC EXAMINATION

Gastrointestinal System

1. Lips, gum, teeth, tongue, oral cavity and tonsils - normal or pigmented.
2. **Abdomen:**
   - **Inspection:** Abdomen is distended, more marked in left upper quadrant.
   - **Palpation:**
     - Liver is enlarged, 5 cm in the midclavicular line from the right costal margin, surface is smooth, margin is sharp, non-tender and firm in consistency.

- Spleen is hugely enlarged, 15 cm from the left costal margin in the anterior axillary line towards the right iliac fossa.
- Kidneys are not ballotable.

♦ **Percussion:** Ascites is absent as evidenced by absence of fluid thrill and shifting dullness.
♦ **Auscultation:** No abnormality detected.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr. …, 40-years-old, farmer, normotensive, nondiabetic, nonsmoker, hailing from …, presented with fever for … months. The fever is intermittent in nature, which persists for 2 to 3 hours, subsides spontaneously, again reappears 2 to 3 times daily. There is no history of chill or rigor, or any sweating. The patient also complaints of substantial loss of weight over last … months despite good appetite. There is no history of diarrhea, vomiting or urinary abnormality. He also complains of heaviness in left upper abdomen and fullness after taking food. For the last ... months, he also noticed blackening of skin involving the whole body. There is no history of cough, hemoptysis, hematemesis, melena or any other bleeding manifestation. For this the patient took paracetamol and some antibiotic prescribed by local physician the name of which he cannot mention.

On examination—general examination (mention as above).

Systemic examination (mention as above).

With this history and physical findings, I have some differential diagnoses:

❖ Malaria.
❖ Kala-azar.
❖ Chronic myeloid leukemia.
❖ Lymphoma.
❖ Others—disseminated tuberculosis, brucellosis, histoplasmosis, schistosomiasis, tropical splenomegaly syndrome.

Q. Why is it spleen and **not kidney**?

A. Differences between spleen and kidney:

Spleen	Kidney
1. It is in the left hypochondrium	1. It is in the lumbar region/loin
2. Moves with respiration towards right iliac fossa	2. Moves downward and forward
3. Well defined medial border	3. Round in shape
4. Notch-present	4. Absent
5. Finger cannot be insinuated between the mass and left costal margin	5. Finger can be insinuated between the mass and left costal margin
6. On percussion—dullness over the mass which is continuous with left lower chest	6. Colonic resonance over the mass
7. Palpable	7. Ballotable

Note

If kidney is hugely enlarged, colonic resonance may be absent and get above the swelling may not be possible.

RELATED QUESTIONS AND ANSWERS

Q. What are the **presentations** of kala-azar?

A. Incubation period is 1 to 2 months (may be months to years, even 10 years).

- Fever—usually intermittent, either double or triple rise daily. Sometimes, fever may be irregular, low-grade continuous, occasionally undulant fever (pyrexia followed by apyrexial period). There may be associated chill and rigor.
- Usually no anorexia, no malaise, no coated tongue.
- Bleeding (due to thrombocytopenia).

Physical findings are:

- Emaciation.
- Anemia (always present, may be severe).
- Splenomegaly which may be huge (firm to hard).
- Hepatomegaly.
- Lymphadenopathy—common in African and Chinese kala-azar, rare in Indian Kala-azar.
- Skin—pigmented, dry thin, scaly. Sometimes there may be diffuse, warty, non-ulcerative skin lesion containing parasite.

Q. What is the **appetite** in Kala-azar?

A. Usually good.

Q. What are the causes of **good appetite but loss of weight**?

A. As follows:

- Diabetes mellitus.
- Thyrotoxicosis.
- Kala-azar.
- Sometimes in malabsorption syndrome.

Organism—Leishmania Donovani complex.

- L. donovani (India and South East Asia).
- L. infantum (Middle East, Mediterranean area).
- L. chagasi (South, Central America).

Source/reservoir—Human (Indian kala-azar).

Mode of transmission:

- Bite by infected female sandfly (common).
- Congenital—transplacental.
- Blood transfusion.

Note Remember the following points:

- Human is the only reservoir in Indian subcontinent.
- Other reservoirs are dog, jackal, fox and wild rodents in other countries.
- Leishmania has two forms - amastigote and promastigote.
- Amastigote form (oval) is found in human, LD body is found in monocyte/macrophage system.
- Promastigote form (flagellate) is found in sandfly, and in culture media.

Q. What **investigations** are done to diagnose kala-azar?

A. As follows:

1. CBC—leukopenia, high lymphocyte and monocyte, neutropenia, absence of eosinophil, thrombocytopenia and high ESR. If CBC is repeated after some days, there is **progressive leukopenia**.
2. Immunological tests, based on antibody:
   - Direct agglutination test (DAT)—it is called DAT because promastigote is used as antigen. May be positive after 2 weeks (usually within month). It remains positive years after cure (so it does not indicate active infection). Disadvantage of DAT—cannot differentiate past, subclinical and active infection. False positive DAT may occur in leprosy, African trypanosomiasis, TB and hepatitis B.
   - Immunochromatographical test (ICT)—also called rapid dipstick rk-39 test.
   - Indirect hemagglutination assay (IHA)
   - Indirect fluorescent antibody test (IFAT)
   - ELISA.
   - Complement fixation test (CFT)—it is nonspecific, positive after 3 weeks. False positive occurs in TB, leprosy, cirrhosis of liver and multiple myeloma. This test is performed by using Kedrowski's bacillus.
   - Aldehyde test—still helpful where there is no facility. This test is non-specific and positive when there is associated hypergammaglobulinemia. It may be false positive in TB, leprosy, cirrhosis of liver, multiple myeloma, SLE, leukemia and thalassemia. This test is positive in kala-azar in 2 to 3 months (negative after 6 months).
3. Detection of antigen—done by latex agglutination test (Katex) for detecting leishmanial antigen in urine. This test is very simple, more specific than antibody-based test, highly sensitive (96%) and also specific (100%). This test indicates active disease. The antigen is detected in urine within a week, disappears from urine within 3 weeks following successful treatment. Hence, this test is helpful for early diagnosis and also to see the response to therapy.
4. Definitive diagnosis by isolation of Leishman-Donovan (LD) body from bone marrow and spleen puncture, also from liver, lymph node and skin lesion. Smears are stained by Leishman, Giemsa or Wright's stain. Culture is done in NNN media (Nicolle-Nove-McNeal). LD body is positive as follows:
   - Spleen—90 to 95% (splenic puncture is avoided in case of soft spleen, prolong prothrombin time (PT) and platelet count is 40,000/mm^3).
   - Bone marrow and liver—85%.
   - Lymph node—65%.
   - LD body is rarely found in peripheral blood in buffy coat preparation. It may also be found in thick film (present in monocyte).
5. PCR (from lymph node or bone marrow aspiration), positive up to 100% case.
6. Blood for total protein and A/G ratio (high total protein, low albumin and high globulin).

Note

Culture is done for identification of species and if the number of organisms are less, it may grow in culture media. Organism may grow after 1 week, may take 4 weeks.

Q. What are the mechanisms of **anemia** in kala-azar?

A. Due to:

- Hypersplenism (which causes sequestration and splenic pooling, destruction of RBC in spleen).
- Short lifespan of RBC
- Hemolysis
- Ineffective erythropoiesis, infiltration of marrow by parasite
- Bleeding, hemodilution.

Q. Why **bleeding** occurs in kala-azar?

A. As follows:

- Bleeding may occur before treatment due to thrombocytopenia
- Bleeding may occur during treatment with sodium stibogluconate.

Q. Why **bleeding** during treatment with sodium stibogluconate?

A. Actual mechanism is unknown. It may be due to:

- Abnormality in preparation of drug
- Decomposed or expired date of drug
- Functional abnormality of platelet by the drug (pentavalent antimony is transformed to trivalent, which may cause thrombasthenia)
- Bleeding due to other causes (CLD and blood dyscrasias).

Q. How to **treat** if there is bleeding?

A. As follows:

- Drug should be stopped
- Platelet count, PT, APTT and liver function tests should be done
- Other causes of bleeding should be looked for
- Symptomatic treatment should be given, may require blood transfusion
- After improvement, drug should be started with low dose, then increase the dose (batch of the drug may be changed). If again bleeding, alternative drug may be given.

Q. What are the **complications** of kala-azar?

A. As follows:

- Secondary infection (pneumonia, tuberculosis)
- Anemia
- Bleeding
- Gastroenteritis, bacillary dysentery
- Liver disease (cirrhosis of liver)
- PKDL
- Rarely, cancrum oris.

Causes of death in Kala-azar—If no treatment is given, patient may die within 1 to 2 year due to:

- Secondary infection
- Bleeding.

Q. How to **treat** kala-azar?

A. As follows:

- Sodium stibogluconate—20 mg/kg for 28 days IV or IM. Can be given in infusion with normal saline. IM injection is very painful, may be given, if any ECG abnormality (arrhythmia or long QT interval).
- Meglumine antimoniate—50 mg/kg is an alternative drug.
- Liposomal amphotericin B—drug of choice, 3 to 4 mg/kg daily, given on days 1 to 5, 14 and 21. May be repeated. Dose for immunoincompetent is 4 mg/kg on day 1 to 5, 10, 17, 24, 31 and 38. It is expensive and not widely available. Preferable to conventional amphotericin B, as it is more effective, less toxic, less protein bound, concentrated and retained in macrophage-rich organs (RE system) other than kidney (not nephrotoxic). Safe in pregnancy.
- Conventional amphotericin B—1 mg/kg for 20 days, given in slow infusion for 4 to 6 hours. It is more protein bound and nephrotoxic.
- New oral drug—miltefosine, a cytotoxic drug, very effective and safe for visceral leishmaniasis. Also helpful in treating resistant kala-azar. Dose is 50 to 100 mg or 2.5 mg/kg daily orally for 28 days (50 mg, if < 25 kg body weight and 100 mg, if > 25 kg body weight). Side effects are less, may cause vomiting, diarrhea, transient raise of serum glutamic pyruvic transaminase (SGPT), blood urea nitrogen (BUN) and creatinine. It has more fetal toxicity, thus not recommended during pregnancy.
- Paromomycin—11 mg/kg/day intramuscularly for 21 days.

Note Remember the following points while treating with sodium stibogluconate:

- Before starting the therapy, perform renal and hepatic function tests, ECG (to see dysrhythmia, prolonged QT and ischemia) and chest X-ray (latent TB, pneumonia).
- During IV injection, if the patient complains of chest pain or cough, stop the drug immediately.
- Monitor ECG, FBC including platelet, hepatic and renal functions.
- The drug should be stopped, if there is bleeding, ECG change (arrhythmia, prolonged corrected QT interval).
- No limitation of dose (previously it was thought that dose should not exceed 1 g /day).

Q. How to see the **response** of therapy?

A. As follows:

- Clinical improvement—improvement of fever, feeling of well-being.
- Reduction in the size of spleen (may take months).
- Weight gain.
- Laboratory findings include increased Hb%, total count of WBC and increased albumin.

Q. What do you mean by **relapse, reinfection** and **resistant** kala-azar?

A. As follows:

- Relapse means after cure, there is again occurrence of kala-azar (usually occurs within 6 months).
- Reinfection following cure, if again kala-azar occurs after 6 months.
- Resistance means no response to drug therapy. It may be primary (no response from beginning of therapy) or secondary (develops later after initial response). It is usually due to insufficient or suboptimal dose or irregular therapy.

Q. How to **treat** if there is **relapse**?

A. Same therapy with sodium stibogluconate for 60 days (double the duration).

Q. How to **treat** a resistant case of kala-azar?

A. In a resistant case of kala-azar, the following therapy should be given:

- Pentamidine isethionate. 3 to 4 mg/kg, 3 times per week for 5 to 25 weeks (at least 5 weeks and 15 injections should be given). Then, sodium stibogluconate 20 mg/kg for 30 days. Pentamidine may cause hypoglycemia, hyperglycemia and shock. It is not used as a first drug, because of more side effects and development of quick resistance.
- Amphotericin B, preferably liposomal amphotericin B.
- Plus adjuvant therapy—γ-interferon, allopurinol, ketoconazole.

Q. How to treat **kala-azar in pregnancy**?

A. Same treatment with sodium stibogluconate. Although the safety of this drug during pregnancy is not established, it should be treated since the disease is potentially dangerous.

Q. What is kala-azar treatment failure **(KATF)**?

A. When kala-azar does not respond to usual therapy with sodium stibogluconate, it is called KATF. It is usually due to inappropriate or suboptimal dose or irregular therapy. Treatment as in resistant kala-azar.

Q. What is **PKDL?**

A. It is a non-ulcerative cutaneous lesion that occurs after successful treatment of visceral leishmaniasis. Initially starts as macules, then erythematous patches, followed by wart-like nodular lesions on the face, ear lobules and limbs. Amastigotes are scanty in the lesion. After treatment, visceral infection disappears, but organisms may remain in skin. After a variable period, skin resistance is lost with resurgence of old infection. Which leads to PKDL.

In Indian subcontinent, it occurs in a small minority of patients 6 months to 3 years or more after the initial infection, creating a persistent human reservoir. They present as macules, papules, nodules (most common) and plaques on the face, mainly around the chin. The face is often erythematous. Hypopigmented macules can occur over all parts of the body and are highly variable in extent and location. There are no systemic symptoms and no spontaneous healing.

In Sudan, about 50% develop skin manifestations of PKDL concurrently with visceral leishmaniasis or within 6 months afterwards. The skin features are as above. In addition, there may be a measles-like micropapular rash all over the body. Children are more frequently affected than in India. Spontaneous healing occurs in about 3/4th cases within 1 year.

Q. What is the **presentation** of PKDL?

A. As follows:

- Multiple, pale, pink, reddish, wart-like, nodules of variable size and shape involving nose, cheek and ear lobule.
- Thick skin.

In early case, depigmented macules, erythematous, well-circumscribed lesions may be seen or all stages of lesions may be present, such as depigmented macules, erythematous lesions and nodules, or only multiple nodules of variable size and shape are seen.

Q. What are the **differential diagnoses** of PKDL?

A. As follows:

- Lepromatous leprosy
- SLE
- Dermatomyositis
- Neurofibromatosis
- Sarcoidosis
- MCTD.

- Others—lipomatosis, acne rosacea, leukemia cutis, secondary syphilis and rhinophyma (irregular thickening of skin of nose with enlarged follicular orifice).

Q. What **investigation** is done to diagnose PKDL?

A. As follows:

- Demonstration of amastigote form of LD body in lesions by slit skin smear and culture. Smear is prepared from nodular lesions (LD bodies are not found in depigmented lesion).
- Immunofluorescence and immunohistochemistry may demonstrate the parasite in skin tissue.
- In the majority of patients, serological tests (direct agglutination test or k39 strip tests) are positive. It is not helpful for diagnosis.

Q. How to **treat** PKDL?

A. As follows:

- In Indian subcontinent, injection sodium stibogluconate (given in cycles) 20 mg/kg daily for 20 days is given. After 10 days interval, the course is repeated. Total 6 cycles are needed with an interval of 10 days. Total 120 injections are needed.
- If a second course is required, it should be given after an interval of two months.
- In Sudan, same injection for 2 months is adequate.
- Alternatively, in India, several courses of amphotericin B infusions may be given.

Note

Pentamidine is ineffective in PKDL.

PYREXIA OF UNKNOWN ORIGIN (PUO)

CHIEF COMPLAINTS

- Fever for ... months
- Weight loss for … months
- Loss of appetite for the same duration.

HISTORY

History of present illness: According to the statement of the patient, he was alright … months back. Since then, he has been suffering from fever which is low grade, continuous, highest recorded temperature is 102° F. There is no history of chill and rigor or profuse sweating. The patient complains of loss of appetite and substantial loss of weight for the last … months. There is no history of diarrhea, vomiting, urinary abnormality, cough, hemoptysis, skin rash, oral ulcer, joint pain, hematemesis, melena, history of travel to malaria endemic zones, IV drug abuse, needle prick injury. He denies unprotected sexual exposure.

History of past illness

Family history

Personal history

Drug history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient is ill and emaciated.
- He is moderately anemic.
- No cyanosis, jaundice, edema, clubbing, koilonychia or leukonychia.
- No lymphadenopathy or thyromegaly.
- Pulse: 120/min.
- BP: 90/70 mm Hg.
- Temperature: 100ºF.

CVS: No abnormality.

Respiratory system: No abnormality.

Nervous system: No neck rigidity, Kernig's sign

Gastrointestinal system: Tongue is coated with angular stomatitis. No organomegaly.

Musculoskeletal system: No spinal tenderness, no gibbus, no other abnormality.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr. …, 42-years-old, businessman, normotensive, nondiabetic, nonsmoker, hailing from …, presented with fever for ... months, which is low grade, highest recorded temperature is 102° F. There is no history of chill and rigor or profuse sweating. The patient complains of loss of appetite and substantial

loss of weight for the last … months. There is no history of diarrhea, vomiting, urinary abnormality, cough, hemoptysis, skin rash, oral ulcer, joint pain, hematemesis, melena, history of travel to malaria endemic zones, IV drug abuse, needle prick injury. He denies unprotected sexual exposure. He was treated by local doctors, but no improvement. There is no family history of any illness.

On examination—general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is pyrexia of unknown origin, which may be due to:

- Tuberculosis.
- Lymphoma.
- Collagen disease (SLE).
- Internal malignancy (in elderly patients).
- Chronic kala-azar.
- Chronic malaria.
- HIV.
- Vasculitis.
- Infective endocarditis.
- Other—hepatic amoebiasis (amoebic liver abscess), adult Still's disease, giant cell arteritis, thyrotoxicosis, myxoma of the heart.

Q. What are the **commonest** causes of PUO?

A. Tuberculosis, collagen disease (e.g. SLE), malignancy (e.g. lymphoma, renal cell carcinoma)

Q. What **investigations** do you suggest?

A. As follows:

1. CBC with ESR, PBF, MP.
2. Blood culture.
3. Blood sugar (to exclude DM).
4. Urine R/E and culture.
5. Chest X-ray P/A view.
6. MT.
7. USG of whole abdomen.
8. If a lymph node or a palpable mass is found—FNAC and/or biopsy.
9. Serum ferritin (high in adult Still's disease).
10. Echocardiography.
11. Autoimmune screen—ANA, ENA, Anti dsDNA, CRP, rheumatiod factor, cANCA, pANCA.
12. HIV screen.
13. Bone marrow examination.
14. Renal function test.
15. Liver function test.
16. Other investigation according to suspicion of cause—CT scan, MRI, PET scan, bronchoscopy, colonoscopy.

RELATED QUESTIONS AND ANSWERS

Q. What is **PUO**?

A. PUO is defined as:

- Fever higher than 38.3°C (101°F) on several occasions.

- Persisting for at least 3 weeks.
- Diagnosis is not made after more than 2 outpatient visits or 3 days in the hospital.

Presently PUO cases are classified in 4 subclasses:

- Classic.
- Nosocomial.
- Neutropenic.
- HIV related.

Types	Definition	Common causes
Classic	Temperature >38.3°C	Infection, malignancy, collagen vascular disease
	Duration of >3 weeks	
	Evaluation of at least 2 outpatient visits or 3 days in hospital	
Nosocomial	Temperature >38.3°C	Clostridium difficile enterocolitis, drug-induced, pulmonary embolism, septic thrombophlebitis, sinusitis
	Patient hospitalized ≥24 hours but no fever or incubating on admission	
	Evaluation of at least 3 days	
Immune deficient (neutropenic)	Temperature >38.3°C	Opportunistic bacterial infections, aspergillosis, candidiasis, herpes virus
	Neutrophil count ≤ 500 per mm^3	
	Evaluation of at least 3 days	
HIV-associated	Temperature >38.3°C	CMV, Mycobacterium avium-intracellulare complex, lymphoma, Pneumocystis jiroveci, Kaposi's sarcoma
	Duration of >4 weeks for outpatients, >3 days for inpatients	
	HIV infection confirmed	

Q. What are the **causes** of PUO?

A. As follows:

1. Infections (30%):
- Tuberculosis.
- Abscess (amoebic or pyogenic liver abscess, subphrenic or at any site).
- Infective endocarditis.
- Urinary tract infection, (especially prostatitis).
- Dental infection.
- Sinusitis.
- Cholecystitis or cholangitis.
- Bone and joint infections.
- Malaria, brucellosis, toxoplasmosis.
- Viral infections (CMV, HIV).
- Fungal infections.

2. Connective tissue disorders (15%):
- SLE.
- Giant cell arteritis.

- Vasculitic disorders, e.g. PAN and rheumatoid disease with vasculitis.
- Polymyalgia rheumatica.
- Adult Still's disease.
- Polymyositis.

3. **Malignancy (20%):**
   - Lymphoma and myeloma.
   - Leukemia.
   - Carcinoma of kidney, liver, colon, stomach, pancreas.
4. **Miscellaneous (20%):**

- Drug fever.
- Atrial myxoma.
- Thyrotoxicosis.
- IBD.
- Liver disease (cirrhosis and granulomatous hepatitis).
- Sarcoidosis.
- Familial mediterranean fever.
- Factitious fever.

5. **Undiagnosed (5 to 15%).** Even in 5% cases, diagnosis may not be possible after postmortem examination.

Q. What are the **drugs causing fever?**

A. As follows:

- Antibiotics, specially beta lactum antibiotics.
- Cardiovascular drugs (quinidine).
- Antineoplastic drugs.
- Drugs acting on CNS (phenytoin).
- Others—methyldopa, barbiturate.

Q. What **history** should be taken in a patient with PUO?

A. As follows:

1. For TB—low grade fever, evening rise, weight loss, night sweat, H/O of contact with tuberculous patient.
2. For other infections:
   - Cough, fever, sputum, chest pain
   - Diarrhea, abdominal pain
   - Dysuria, frequency, urgency, burning micturition
   - Place of residence and overseas travel (malaria, kala-azar, amoebiasis)
   - History of sexual exposure (HIV, Venereal disease, PID)
   - Contact with domestic or wild animals (psittacosis, brucellosis, Q-fever, leptospirosis).
3. For collagen diseases:
   - Skin rash
   - Mouth ulcer
   - Joint pain
   - Alopecia.
4. Unilateral headache, arthralgia, myalgia (giant cell arteritis, polymyalgia rheumatica).
5. Occupation (farming, veterinary surgeon, etc.).
6. Drug history to exclude drug fever.
7. History of any intervention, e.g. catheterization, A-V fistula, prosthetic valve, colonoscopy.

Q. What **physical findings** should be look for in a patient with PUO?

A. As follows:

1. Pattern of temperature.
2. Skin rash—Erythema nodosum, erythema multiforme, vasculitis rash.
3. Hand—Stigmata of infective endocarditis, rheumatoid arthritis, dermatomyositis, clubbing, puncture marks (I/V drug abuse, HIV, HBV, etc.).
4. Lymph node—Epitrochlear, axillary, cervical, inguinal.
5. Eye—Iritis, conjunctivits to exclude seronegative arthritis, collagen disease, sarcoidosis.
6. Face—Butterfly rash to exclude SLE, heliotrope rash for dermatomyositis, lupus pernio and bilateral parotid enlargement for sarcoidosis.
7. Mouth—Ulcer, gum disease, tooth, tonsil.
8. Thyroid to exclude subacute thyroiditis.
9. Chest—Bony tenderness, murmur (SBE, myxoma), prosthetic valve.
10. Abdomen—Tenderness over the liver (liver abscess, sub-diaphragmatic abscess), spleen, per rectal examination to exclude prostatic abscess, Ca- prostate.
11. Nervous system—Look for signs of meningism, focal neurological signs.
12. Fundus—Roth's spot (SBE), retinal hemorrhage or infarction (leukemia).

TAKAYASU'S DISEASE

CHIEF COMPLAINTS

- Fever for ... months
- Pain in multiple joints for … months
- Weakness of upper limbs for … months
- Loss of weight for … months.

HISTORY

History of present illness: According to the statement of the patient, she was alright … months back. Since then, she has been suffering from fever which is low grade, continued and not associated with chill, rigor or sweating. She also complains of mild to moderate pain in multiple joints including small joints of hands, wrists, elbows, knees and ankles. There is no history of swelling of the joints or morning stiffness. For last … months, she complains of weakness of both upper limbs. She noticed pain in both upper limbs which appears after 10 to 15 minutes of manual work and subsides after taking rest. The patient also complains of loss of appetite and substantial weight loss for the last ... months. There is no history of cough, chest pain, breathlessness, pain abdomen, bleeding manifestation, oral ulcer or skin rash. Her bowel and bladder habits are normal.

History of past illness: Mention according to the patient's statement.

Family history: Mention according to the patient's statement.

Personal history: Mention according to the patient's statement.

Drug history: She was treated with paracetamol, ciprofloxacin, injection ceftriaxon but no response.

GENERAL EXAMINATION

- The patient is ill looking and emaciated.
- Mildly anemic.
- No cyanosis, jaundice, edema, clubbing, koilonychias or leukonychia.
- No lymphadenopathy or thyromegaly.
- No skin rash.
- Pulse: All peripheral pulse in upper limbs are absent. In the lower limbs, pulse is present, 88/min, regular.
- BP: Not recordable in upper limbs.
- Temperature: 99ºF.
- Bruit is present over both carotids.

SYSTEMIC EXAMINATION

Cardiovascular System

1. Peripheral pulse: All peripheral pulse in upper limbs are absent. In the lower limbs, pulse is present, 88/min, regular.
2. BP: Not recordable in upper limbs. (It should be recorded in the lower limb with 18 cm cuff).
3. JVP: Not raised.
4. Precordium:
   - Inspection—There is no visible cardiac impulse

- Palpation—Apex beat is in right 5th intercostal space, 9 cm from midline, normal in character. There is no thrill.
- Auscultation—Both first and second heart sounds are normal and audible in all areas. There is a high pitched, blowing, early diastolic murmur best heard in the left lower parasternal area, with patient bending forward and breathing hold after expiration. There is no added sound.

Locomotor System

- There is no swelling of any joint.
- Small joints of hands, wrists and elbows are mildly tender.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Ms. …, 25-years-old, student, normotensive, nondiabetic, nonsmoker, hailing from …, presented with fever for … months, which is low grade, continued and not associated with chill, rigor or sweating. She also complains of mild to moderate pain in multiple joints including small joints of hands, wrists, elbows, knees and ankles. There is no history of swelling of the joints or morning stiffness. For last … months, she complains of weakness of both upper limbs. She noticed pain in both upper limbs which appears after 10 to 15 minutes of manual work and subsides after taking rest. The patient also complains of loss of appetite and substantial weight loss for the last ... months. There is no history of cough, chest pain, breathlessness, pain abdomen, bleeding manifestation, oral ulcer or skin rash. Her bowel and bladder habits are normal. There is no family history of such illness. She was treated with some drug by local doctor, the name of which she can not mention.

On examination—general examination (mention as above).

Systemic examination (mention as above).

My diagnosis is Takayasu's arteritis.

Q. Why Takayasu's disease?

A. Because all the pulses in the upper limbs are absent and there is carotid bruit.

Q. What **investigations** should be done in Takayasu's disease?

A. As follows:

- CBC (high ESR and normocytic normochromic anemia).
- Chest X-ray shows cardiomegaly and widening of aorta.
- Aortography of aortic arch and its branches, renal angiogram shows narrowing, coarctation and aneurismal dilatation.
- Serum immunoglobulin is high.

Q. What are the causes of **absent radial pulse**? Or unequal radial pulse?

A. As follows:

- Anatomical aberration (may be congenital).
- Atherosclerosis.
- Co-arctation of the aorta (before origin of the left subclavian artery).
- Takayasu's arteritis.
- Iatrogenic—blalock taussig shunt (done in TOF), AV fistula for hemodialysis.
- Occlusion by thrombosis.
- Occlusion of the subclavian artery by cervical rib or neoplasm.
- Dissecting aneurysm.

RELATED QUESTIONS AND ANSWERS

Q. What is **Takayasu's disease** (pulseless disease or aortic arch syndrome)?

A. It is a chronic inflammatory, granulomatous panarteritis of unknown cause involving the elastic arteries. It commonly involves aorta and its major branches, carotid, ulnar, brachial, radial and axillary. Occasionally, may involve pulmonary artery, rarely abdominal aorta, renal artery resulting in obstruction. Age of onset is 25 to 30 years. Common in female, F:M ratio is 8:1.

Q. What are the **pathological changes** in Takayasu's diseases?

A. Panarteritis, with inflammatory mononuclear cell infiltration with occasional giant cell. There is intimal proliferation and fibrosis, scaring and vascularization of media and disruption and degeneration of the elastic lamina. Narrowing of the lumen occurs with or without thrombosis.

Q. What are the **types** of Takayasu's disease?

A. 4 types:

- Type 1 – localized to the aorta and its branches.
- Type 2 – localized to descending thoracic and abdominal aorta.
- Type 3 – combined features of type 1 and 2.
- Type 4 – involves the pulmonary artery.

Q. What are the **clinical features**?

A. Common in adolescent girls and young women (F:M = 8:1), 25 to 30 years, more in Asians. Clinical features are:

- General symptoms are—fever, malaise, weight loss, arthralgia, myalgia, dizziness, giddiness, headache, syncope, seizure, claudication in the upper limb.
- There may be arotic regurgitation, renal artery stenosis or anginal pain. Hypertension in 32 to 93%. There may be pericarditis, myocardial infarction, congestive cardiac failure, etc.

Q. What are the **ophthalmologic** findings?

A. Ophthalmologic examination may show retinal ischemia, retinal hemorrhages, cotton-wool exudates, venous dilatation and beading, microaneurysms of peripheral retina, optic atrophy, vitreous hemorrhage and classic, wreath like peripapillary arteriovenous anastomoses.

Q. What is the **treatment**?

A. As follows:

- High dose corticosteroid—prednisolone 40 to 60 mg daily or 1 to 2 mg/kg.
- If refractory to steroid or difficult to taper steroid, methotrexate up to 25 mg weekly.
- Reconstructive vascular surgery in selected case.

Prognosis—with appropriate treatment, 5 year survival is 83%.

PUO (HIV/AIDS)

CASE NO. 1

Presenting complaints:

- Fever for … months
- Passage of loose stool for … months
- Weight loss, weakness for … months.

HISTORY

History of present illness: According to the patient's statement, he was reasonably well … months back. Since then, he has been suffering from low grade continued fever, mostly associated with evening rise. The fever is not associated with chills and rigor or sweating. He also complains of alteration of bowel habit with predominantly large volume watery diarrhea, not mixed with mucus or blood, without any tenesmus. It is associated with mild constant dull, diffuse abdominal pain without any radiation. He agreed frequent attack of sore throat and pain on swallowing for … months. The patient also complains of marked loss of weight, weakness and loss of appetite for last … year. There is no history of cough, hemoptysis, urinary abnormality, polyarthritis, and mouth ulcer or skin rash.

History of past illness: He also gives history of a severe form of flu like illness 3 years back, manifested as fever with rash, severe sore throat, neck swelling, and generalized body ache. Since then he suffered several episodes of diarrhea, which persisted for prolonged period and recurrent episodes of pneumonia, which were treated with antibiotics.

Family history: He is from middle class family and his monthly income aground 5000 taka per month.

Personal history: The patient agreed unsafe sexual practice with multiple partners. He is alcoholic and smoker. There is no history of injectable drug abuse, needle sharing or transfusion of blood or blood product.

Treatment history: He was treated with multiple antibiotics, metronidazole.

Socioeconomic history: He is from middle class family and his monthly income around 5000 take per month.

GENERAL EXAMINATION

- The patient is ill looking and emaciated.
- Mildly anemic.
- Pitting edema is present.
- No cyanosis, jaundice, clubbing, koilonychias or leukonychia.
- Generalized lymphadenopathy of variable size and shape involving anterior cervical, posterior cervical and inguinal. Some are matted some are discreet. These are non tender, firm in consistency, free from underlying structure and overlying skin.
- No thyromegaly.

- No skin rash.
- Pulse: 88/min, regular.
- BP: 100/60 mm Hg.
- Temperature: 99ºF.

SYSTEMIC EXAMINATION

Gastrointestinal System

Lips, gum, teeth—normal.

Oral cavity:

- White patches on buccal mucosa, tongue, palate and pharynx (oropharyngeal candidiasis).
- Corrugated white plaques running vertically on the side of the tongue (oral hairy leukoplakia—mention if any).

Abdomen:

1. Inspection – Normal.
2. Palpation—
   - Liver is palpable … cm from costal margin on right midclavicular line, firm in consistency, sharp lower margin, non-tender, smooth surface.
   - Spleen is enlarged, … cm from left costal margin in anterior axillary line towards right iliac fossa, firm in consistency, rounded margin, smooth surface, non-tender.
   - Kidneys are not palpable.
   - Renal angles are non-tender.
3. Percussion—No abnormality.
4. Auscultation—No abnormality.

Examination of other systems reveals no abnormalities.

SALIENT FEATURES

Mr …, 45-years-old, normotensive, nondiabetic, smoker and alcohol abuser, presented with low grade continued fever for … months. It is mostly associated with evening rise, but not with chills and rigor or sweating. He also complains of alteration of bowel habit with predominantly large volume watery diarrhea, not mixed with mucus or blood, without any tenesmus. It is associated with mild constant dull, diffuse abdominal pain without any radiation. He agreed frequent attack of sore throat and pain on swallowing for … months. The patient also complains of marked loss of weight, weakness and loss of appetite for last … year. There is no history of cough, hemoptysis, urinary abnormality, polyarthritis, and mouth ulcer or skin rash.

He also gives history of a severe form of flu like illness 3 years back, manifested as fever with rash, severe sore throat, neck swelling, and generalized body ache. Since then he suffered several episodes of diarrhea which persisted for prolonged period and recurrent episodes of pneumonia which were treated with antibiotics.

The patient agreed unsafe sexual practice with multiple partners. He is alcoholic and smoker. There is no history of injectable drug abuse, needle sharing or transfusion of blood or blood product.

He was treated with multiple antibiotics, metronidazole but without any response.

On examination—general examination (mention as above).

Systemic examination (mention as above).

This patient has fever, bowel abnormality with generalized lymphadenopathy and hepatosplenomegaly for which I have some differential diagnoses:

- Disseminated tuberculosis.
- Kala-azar.
- Malaria.
- Lymphoma.
- Collagen disease like SLE.
- Toxoplasmosis.
- Brucellosis.
- HIV infection.
- Others—fungal infection (histoplasmosis, coccidioidomycosis), chronic cryptosporidial diarrhea.

Q. Why **lymphoma?**

A. The patient has history of fever, night sweating and weight loss over several months, also there are lymphadenopathy and hepatosplenomegaly.

Q. Why **disseminated tuberculosis?**

A. The patient has history of fever, night sweating and weight loss over several months, also there are lymphadenopathy and hepatosplenomegaly. TB is endemic in patient's country of origin.

CASE NO. 2

Chief complaints:

- Fever for ... months.
- Weight loss for … months.
- Loss of appetite for … months.

History of present illness:

According to the statement of the patient, he was alright … months back. Since then, he has been suffering from fever which is continued low grade. It is not associated with chill and rigor or profuse sweating. He also complains of loss of appetite and substantial loss of weight for the last … months. There is no history of diarrhea, vomiting, urinary abnormality, cough, hemoptysis, skin rash, oral ulcer, joint pain, hematemesis, melena, history of travel to malaria endemic zones, IV drug abuse, needle prick injury. He denies unprotected sexual exposure.

He was treated by local doctors with several antibiotics, but no response. Laboratory investigations showed low hemoglobin and high ESR. Other investigations such as urine, blood C/S, chest X-ray, ultrasonogram of abdomen, MP, ICT for kala-azar—all were negative.

Two weeks later, the patient noticed a mass on the left side of the neck. Examination revealed cervical lymphadenopathy, which are firm, matted, non-tender. FNAC of the lymph node showed caseating granuloma consistent with tuberculosis. Antitubercular treatment with 4 drugs was prescribed with other supportive care. The patient was reviewed after 1 month, but his condition was deteriorating. Again all other investigations were done and all were negative. He denied any sexual abuse, travel abroad, etc. On suspicion, HIV antibody was done and it was found to be positive.

History of past illness

Family history

Personal history

Drug history: Mention according to the patient's statement.

GENERAL EXAMINATION

- The patient is ill and emaciated.
- He is moderately anemic.
- No cyanosis, jaundice, edema, clubbing, koilonychia or leukonychia.
- There are left sided cervical lymphadenopathy, which are firm, matted, non-tender, not attached to overlying skin or underlying structure, no sinus.
- Pulse: 120/min.
- BP: 120/75 mm Hg.
- Temperature: 100ºF.

CVS—No abnormality.

Respiratory system—No abnormality.

Nervous system—No neck rigidity, Kernig's sign

Gastrointestinal system—Tongue is coated with angular stomatitis. No organomegaly.

Musculoskeletal system—No spinal tenderness, no gibbus, no other abnormality.

Examination of other systems reveals no abnormalities.

My diagnosis is HIV with tubercular lymphadenitis.

RELATED QUESTIONS AND ANSWERS

Q. What is **HIV**?

A. Human Immunodeficiency virus (HIV) is a single stranded RNA virus, belongs to the lentivirus group of retrovirus family. Two types—HIV-1 and HIV-2.

HIV disease—It is the spectrum of disorders ranging from primary infection, with or without the acute HIV syndrome, to the asymptomatic infected state to advanced disease.

Q. What is **AIDS?**

A. HIV infected individual with CD4 T cell count <200 cells/mm^2 regardless of the presence of the symptoms or HIV infected individual with AIDS defining conditions (category C) regardless of CD4 count is labeled AIDS.

Q. What is the **mode of transmission** of HIV?

A. As follows:

1. Sexual contact with an infected person—more in homosexuals, multiple sexual partners and non-circumcised persons.
2. Transplacental, perinatal exposure and breastfeeding.
3. Parenteral exposure to infected body fluid—
   - Sharing of needles, including intravenous drug abuser.
   - Blood and blood product transfusion.
   - Occupational transmission.
   - Organ transplantation including cornea.

Routes not involved in transmission:

- Close personal contact (sleeping, shaking hands, kissing, etc).
- Social contact (e.g. at school, swimming pool, shopping mall).
- Sharing toilet.
- Staying in a common ward in hospital.
- Sharing utensils.
- Insect or animal bite.
- Respiratory droplets, sputum, etc.
- Through health-workers like doctors, nurse, etc.

Q. What is the **natural history** of HIV or AIDS?

A. Natural history is as follows:

1. **Primary infection—**It is symptomatic in 70 to 80% of cases and usually occurs 2 to 6 weeks after exposure. Features are:
   - Fever with rash
   - Pharyngitis with cervical lymphadenopathy
   - Myalgia, arthralgia
   - Headache
   - Mucosal ulceration.
2. **Asymptomatic infection—**The patient remains asymptomatic but potentially infectious to others. This stage may persist for 5 to 10 years. Laboratory investigations may show anemia, leukopenia, lymphopenia and reduced CD4 count. Also cutaneous anergy.
3. **Mildly symptomatic disease** (HIV symptomatic or indicator diseases, category B):
   - Constitutional—Low grade fever, night sweats, weight loss.
   - Oral hairy leukoplakia.
   - Recurrent oropharyngeal candidiasis, recurrent vaginal candidiasis.
   - Herpes zoster involving more than 1 dermatome.
   - Idiopathic thrombocytopenic purpura.
   - Chronic diarrhea, bacillary angiomatosis.
   - Peripheral neuropathy.
   - Cervical dysplasia, severe pelvic inflammatory disease.
4. **Acquired immunodeficiency syndrome:** AIDS-defining diseases are (category C) –
   - Esophageal candidiasis.
   - Cryptococcal meningitis.
   - Chronic cryptosporidial diarrhea.
   - Cerebral toxoplasmosis.
   - CMV retinitis or colitis.
   - Chronic mucocutaneous herpes simplex.
   - Disseminated *Mycobacterium avium intracellulare* (MAI).
   - Pulmonary or extrapulmonary tuberculosis.
   - *Pneumocystis jirovecii* (*carinii*) pneumonia.
   - Progressive multifocal leucoencephalopathy.
   - Recurrent non-typhi *Salmonella* septicemia.
   - Extrapulmonary coccidioidomycosis.
   - Invasive cervical cancer.
   - Extrapulmonary histoplasmosis.
   - Kaposi's sarcoma.
   - Non-Hodgkin's lymphoma (including Burkitt's lymphoma).
   - Primary cerebral lymphoma.

- HIV-associated wasting.
- HIV-associated dementia.

Clinical category of HIV:

CD 4 count (/ cmm)	**Category A.** Asymptomatic or persistent generalized lymphadenopathy or acute seroconversion illness	**Category B:** (see above)	**Category C:** (see above)
> 500	**A1**	**B1**	**C1**
200 to 499	**A2**	**B2**	**C2**
<200	**A3**	**B3**	**C3**

Note

Category C, A3, B3 (shaded area) indicates AIDS.

Q. Name some **common infections** in AIDS.

A. As follows:

- *Pneumocystis jiroveci.*
- *Candida albicans.*
- *Cryptococcus neoformans.*
- *Toxoplasma gondii.*
- *Mycobacterium* (typical and atypical).
- CMV.
- Amebiasis.
- *Cryptosporidium.*

Q. Name some **HIV related cancer.**

A. As follows:

- AIDS defining cancers—Kaposi's sarcoma and non-Hodgkin's lymphoma.
- Non-AIDS defining malignancies—Anal cancer and Hodgkin's disease.

Q. What is the correlation between **CD4 count and HIV associated diseases?**

A. As follows:

- **> 500 cells/mm^3**—acute primary infection, recurrent vaginal candidiasis, persistent generalized lymphadenopathy.
- **< 500 cells/mm^3**—pulmonary tuberculosis, herpes zoster, oropharyngeal candidiasis, oral hairy leukoplakia, Kaposi's sarcoma, HIV-associated idiopathic thrombocytopenic purpura, cervical intraepithelial neoplasia II and III.
- **< 200 cells/mm^3**—*pneumocystis jiroveci pneumonia*, mucocutaneous herpes simplex, esophageal candidiasis, miliary or extrapulmonary tuberculosis.
- **< 100 cells/mm^3**—cerebral toxoplasmosis, cryptococcal meningitis, non-Hodgkin's lymphoma, progressive multifocal leucoencephalopathy, HIV-associated dementia.
- **<50 cells/mm^3**—CMV retinitis, CMV gastrointestinal disease, primary CNS lymphoma, disseminated MAI (*Mycobacterium avium intracellulare*).

Q. What are the **cutaneous manifestations** of HIV?

A. As follows:

- Early HIV—Herpes simplex, varicella zoster, human papilloma virus.
- Late HIV—Kaposi's sarcoma, molluscum contagiosum, chronic mucocutaneous herpes simplex.

Q. What are the findings in **mouth cavity** in HIV patient?

A. Hairy leukoplakia, oropharyngeal candidiasis, aphthous ulcer, herpes simplex, periodontal disease.

Q. What are the causes of **diarrhea or enteropathy** in HIV patient?

A. Common organisms are:

- Cytomegalovirus (CMV).
- Cryptosporidium and microsporidium.
- *Mycobacterium avium intracellulare* (MAI).
- Other infections—*Isospora*, *Giardia*, *Entamoeba histolytica*, *Salmonella*, adenovirus and bacterial overgrowth, etc.

The patient presents with dysphagia, retrosternal pain, watery diarrhea often accompanied by blood, colicky abdominal pain, weight loss and fever.

Q. What are the major causes of **pulmonary disease** in HIV?

A. As follows:

- Pneumocystis jiroveci pneumonia, tuberculosis, bacterial pneumonia, fungal infection (e.g. histoplasma), cryptococcus.
- Malignancy—non-Hodgkin's lymphoma, Kaposi's sarcoma.

Note

TB in HIV usually involves the lower lobes and cavitation is uncommon.

Q. Name some **neurological manifestations** in AIDS patients.

A. As follows:

- Acute meningitis—during acute seroconversion. May be aseptic meningitis, multiple cranial nerve palsy, etc.
- Encephalitis—herpes simplex, varicella zoster virus.
- *Toxoplasma gondii* causes encephalitis characterized by headache, confusion, convulsion and focal signs. MRI shows multiple ring-enhancing lesions in cortical grey-white matter interface, basal ganglia or brain stem with edema and mass effect. Retinitis may coexist.
- Primary CNS lymphoma (5%).
- AIDS dementia complex (ADC)—may precede the diagnosis of AIDS in 25% cases.
- Progressive multifocal leucoencephalopathy (PML)—presents with hemiparesis, visual or speech defects, altered mental status, ataxia. Seizures are rare and fever is absent. MRI shows non-enhancing white mater lesions without edema.
- Retinitis—CMV, toxoplasmosis.
- Autonomic neuropathy.
- Spinal cord, root and peripheral nerve disease includes:
  - Vacuolar myelopathy—presents with spastic paraparesis and sensory ataxia. There is involvement of lateral and posterior column of spinal cord.
  - Peripheral neuropathy—by HIV or drugs.
  - Other—Guillain-Barré syndrome, transverse myelitis, brachial neuritis, polyradiculitis and peripheral neuropathy.

Q. What are the causes of **seizure** in HIV positive patient?

A. HIV encephalopathy, cerebral toxoplasmosis, cryptococcal meningitis, primary CNS lymphoma, PMLE.

Q. What are the **ocular** diseases in AIDS?

A. Commonly there is CMV retinitis. Fundoscopy shows retinal cotton wool spots, sometimes fluffy white retinal lesions with area of hemorrhage. Other cause of retinitis is—*Toxoplasma gondii*.

Q. What are the **renal, cardiac and endocrine complications of** HIV?

A. As follows:

1. Renal:
- Acute renal failure due to acute infection, drug toxicity.
- Chronic renal failure due to HIV-associated nephropathy (HIVAN).
- HIV immune complex kidney diseases.
- Thrombotic microangiopathy.

2. Cardiac disease:
- Dilated cardiomyopathy.
- Zidovudine induced cardiomyopathy.
- HIV patients are at higher risk of coronary artery disease. It may be due to HIV itself and change of lipid by antiretroviral drugs.

3. Endocrine: Hypoadrenalism, hypogonadism, hypopituitarism.

Q. What are the **Hematological** complications in HIV?

A. It occurs in advanced HIV infection.
- Anemia—usually mild, normocytic normochromic, causes are anemia of chronic disorder, bone marrow suppression or infiltration, malabsorption, side effect of drug, etc.
- Leukopenia (neutropenia is common, also lymphopenia).
- Thrombocytopenia, may occur early and may be the only manifestation in early case.
- Lymphoma.
- Pancytopenia (may be due to underlying opportunistic infection, malignancy, *Mycobacterium avium intercellulare*, disseminated CMV, lymphoma).

Q. What are the **baseline investigations** for newly diagnosed (asymptomatic patient) HIV infected patients?

A. As follows:

1. Routine tests—CBC, PBF, LFT, renal function test, lipid profile, blood glucose, urinalysis, chest X-ray.
2. Related to HIV:
   - HIV antibody (confiramatory).
   - HIV rapid antibody test (result in 10 to 20 minutes). Should be confirmed with ELISA and Western blot.
   - CD4 count.
   - Viral load.
   - HIV genotype.
3. For other infections:
   - Hepatitis serology (A, B, C), HCV - RNA.
   - Cytomegalovirus serology, PCR.
   - Toxoplasmosis serology.
   - Syphillis serology.
   - Screening for other sexually transmitted disease.
   - Cryptococcal antigen.
4. Others:
   - Cervical cytology in women.
   - Lymphocyte subsets.

- HLA-B*5701 screen for hypersensitivity to abacavir.
- Fundoscopy.

Q. How to **diagnose** HIV or AIDS?

A. Screening by ELISA (positive 3 to 12 weeks after infection), confirmation by Western blot.

Q. What are the **pre-test and post-test counseling** for suspected HIV/AIDS patients?

A. As follows:

Pre-test counseling:

- Purpose of the test should be discussed.
- Assessment of the risk factors.
- Explanation of the natural history of HIV to the patient.
- Discussion about mode of transmission and reduction of risk.
- Coping strategy.
- Explanation of the test procedure.
- Informed consent.

Post-test counseling:

1. If the test result is negative:
   - Discussion regarding behavior modification including safer sex and needle exchange.
   - A second test should be carried out 3 months after last exposure.
2. If the test result is positive:
   - Explanation of significance and implications of result.
   - Urgent medical follow-up.
   - Strategy regarding fear of disclosure and social rejection.
   - Verbal and written information.
   - Emotional and practical support by providing phone number and name.

Q. What are the **immunizations** that should be offered to every HIV infected patients?

A. As follows:

- Hepatitis A and hepatitis B, if non-immune.
- Pneumovax (at initial diagnosis and then 3 to 5 yearly).
- Influenza (yearly).
- Tetanus booster (if injection drug-user).

Q. What are the **aims of treatment?**

A. The aims of HIV treatment are to:

- Reduce the viral load to an undetectable level for as long as possible.
- Improve the CD4 count to > 200 cells/mL, so that severe HIV related disease become unlikely.
- Improve the quantity and quality of life without unacceptable drug-related side-effects or lifestyle alteration.
- Reduce transmission.

Q. What are the **indications** of antiretroviral therapy in patients with HIV infection?

A. As follows:

1. Acute infection syndrome.
2. Chronic infection:
   - Symptomatic disease (including HIV-associated nephropathy).
   - Asymptomatic diseases:
     - CD4+ T cell count <350/μL.
     - Pregnancy.
3. Postexposure prophylaxis.

Q. What are the indications to start **HAART (highly active anti-retroviral therapy)** on the basis of CD4 count?

A. As follows:

- Seroconversion—consider treatment, if neurological presentation, CD4 count < 200 cells/mm^3 for > 3 months or AIDS diagnosis.
- CD4 count ≥350—monitor 3 to 6 monthly (consider treatment if hepatitis B or C co-infected or > 55 years of age).
- CD4 count 201 to 350—treat as soon as the patient is ready.
- CD4 count <200—treat as soon as possible.
- AIDS defining diagnosis—treat as soon as possible (except for TB, if CD4 > 350 cells/mm^3).

Q. How to **treat** AIDS?

A. As follows:

General management:

- Dietary and nutritional advice should be given.
- Advice on smoking, alcohol, drug misuse and exercise should be given.
- Proper advice on reducing the risk of HIV transmission including sexual practice must be provided.
- Psychological support is a must for the patient, family, friends and care-givers.
- Information about childbearing must be discussed.

Drug treament:

Drug treatment depends on clinical assessment, laboratory investigations including viral load and CD4 counts, also individual circumstances.

Q. Name the **drugs** used in HIV infected patients.

A. Drugs used in HIV infected patients are:

1. Reverse transcriptase inhibitors (RTI):
   - Nucleoside reverse transcriptase inhibitors (NRTIs)—zidovudine, didanosine, lamivudine, stavudine, abacavir and emtricitabine.
   - Non-nucleoside reverse transcriptase inhibitors (NNRTIs)—nevirapine, efavirenz and etravirine.
2. Protease inhibitors (PIs)—indinavir, ritonavir, lopinavir, tipranavir, atazanavir, fosamprenavir and darunavir.
3. Entry inhibitors:
   - Fusion inhibitors—enfuvirtide.
   - Co-receptor blockers—maraviroc.
4. Integrase inhibitors—raltegravir.

Q. When antiretroviral **therapy should be changed?**

A. Antiretroviral therapy should be changed in following conditions:

- Drug side-effects (early or late).
- Difficulties in adherence.
- Virological failure.
- Persistently declining CD4 plus T cell numbers.
- Clinical deterioration.

Q. When will you **stop treatment?**

A. HAART should be stopped in the following conditions:

- Drug toxicity.

- Potential drug interaction with other drugs used for other more serious illness.
- Poor compliance.
- Patient's unwillingness to take drugs.

Q. How will you **monitor** a patient taking HAART?

A. As follows:

- Clinical history and examination
- Weight
- HIV viral load
- Lymphocyte subset
- Full blood count
- Liver and renal function
- Fasting lipid profile
- Blood glucose.

Q. What is the treatment of **CMV retinitis** in a patient with HIV?

A. Ganciclovir. The usual adult dose is:

1. Induction therapy—5 mg/kg IV for 1 hour, 12 hourly for 14 to 21 days.
2. Maintenance therapy:
   - 5 mg/kg IV for 1 hour daily, 7 days/week. Or, 6 mg/kg IV daily, 5 days/week.
   - Oral—1000 mg 3 times a day. Or, 500 mg 6 times a day (every 3 hours while awake) with food.
3. If there is progression of CMV retinitis during maintenance treatment, reinduction should be given.

Q. How will you **prevent HIV infection?**

A. As follows:

- Safe sexual practice.
- Effective treatment of STI.
- Screening of blood and blood products.
- Use of clean needles and syringes for IV drug abuser.
- Anti-retroviral drugs to reduce mother to child transmission.

Q. How will you treat a person **exposed to HIV infection** (postexposure prophylaxis)**?**

A. When risk is significant, in both occupational and non-occupational settings, lopinavir, tenofovir and emtricitabine are given. The first dose given as soon as possible, preferably within 6 to 8 hours. 4 weeks of therapy is recommended. Protection is not absolute and seroconversion may occur.

Q. How will you treat a **HIV positive pregnant woman?**

A. As follows:

1. Antepartum:
   - Ritonavir-boosted PI (e.g. lopinavir) with zidovudine and lamivudine from 20 weeks given to all mothers.
   - Or, oral zidovudine monotherapy for those with viral loads < 10000 copies/mL and wild-type virus who are willing to have cesarean section.
2. During delivery:
   - ZDV IV infusion at the onset of labor given to those on ZDV alone or those on HAART but with detectable virus, undergoing normal vaginal delivery.
   - Delivery by cesarean section reduces the risk of transmission, but if the patient is on HAART is unnecessary.
3. After delivery:

- The neonate should get oral zidovudine for 6 weeks.
- Breastfeeding should be avoided.

PNEUMOCYSTIS JIROVECI PNEUMONIA (PCP)

Pneumocystis jiroveci (previously Pneumocystis carinii) is an opportunistic fungus that causes pneumonia in HIV or AIDS patients, when CD4 is <200/cmm. PCP may also occur in patients who are immunosuppressed due to cancer, corticosteroids or other immunosuppressive drugs, organ or bone marrow transplantation, etc. In a few patients, it may also infect other organs like liver, spleen and kidneys.

The organism damages alveolar epithelium, causing interstitial plasma cell pneumonia with foamy exudate in the alveoli that impedes gas exchange and reduces lung compliance.

Clinical features – develops slowly over weeks, may take months.

- Initially there is shortness of breath on exertion.
- Cough (usually dry).
- Fever, malaise, weight loss and night sweat.
- Tachypnea, tachycardia, cyanosis.
- Fine crepitations may be heard on auscultation.

Investigations:

- Chest X-ray—typically bilateral perihilar interstitial infiltrates, which can progress to confluent alveolar shadows through out the lungs. Usually sparing of apex and costphrenic angle (X-ray may be normal in early infection).
- HRCT of chest (shows ground glass appearance).
- Sputum for cytology or PCR—organism may be found in 50 to 90% cases (by silver or Giemsa staining or immunofluorescent technique. Organism cannot be cultured).
- Bronchoscopy and bronchoalveolar lavage (shows organisms in 90 to 95% cases).
- Blood gases analysis (Po_2 is low, <90% on exercise).
- PCR amplification of the fungal DNA in blood.
- Lung function tests—restrictive pattern with reduced diffusion capacity.
- Lung biopsy (shows thickened alveolar septa with fluffy eosinophilic exudate in the alveoli. Immunofluorescent or histochemical staining or molecular analysis of PCR products can confirm pneumocystis infection).
- LDH—high.

Note Remember the following points:

- PCP is confirmed by identification of the organism in sputum or bronchoalveolar lavage. Silver stain or immunofluorescence technique is used to demonstrate characteristic cysts, which resemble crushed ping-pong balls and are present in aggregates of 2 to 8.
- Pneumocystis jiroveci may be present in the lungs of normal healthy individual. So detection of the organism in sputum or BAL does not mean that the patient is suffering from PCP or AIDS.

Complications:

- Respiratory failure
- Pneumothorax

- Pleural effusion (rare)
- Bacterial superinfection.

Treatment—should be given as early as possible.

- IV co-trimoxazole (120 mg/kg daily in divided doses for 21 days) is the first line treatment.
- If sensitive to co-trimoxazole, IV pentamidine (4 mg/kg/day) or dapsone and trimethoprim are given for the same duration.
- Atovaquone or combination of clindamycin and primaquine may be given.
- Prednisolone—40 mg bid for 5 days, then 40 mg daily for 5 days and 20 mg daily for 11 days is given.
- Systemic corticosteroids may be used in severe cases (especially if PO2 < 9.5 kPa).
- CPAP or mechanical ventilation (if patient remains severely hypoxic or becomes too tired).

Prognosis:

- May cause death from respiratory failure. Short term corticosteroid may reduce death in AIDS patients with moderate to severe pneumocystis pneumonia.

Prophylaxis—secondary prophylaxis is indicated in patients who recovered from PCP and CD4 remain <200/cmm. The usual regimen is co-trimoxazole 960 mg three times a week. Patients sensitive to sulphonamide are given dapsone, pyrimethamine or nebulized pentamidine.

Primary prophylaxis therapy is recommended in:

- AIDS and CD4 counts < 200/cmm.

Note Other conditions where prophylaxis therapy is required:

- Bone marrow or organ transplant recipients.
- Patient getting long-term, high-dose corticosteroids.

It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has.

Sir William Osler

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